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Box 5264
PTO/SB/05 (2/98)**UTILITY
PATENT APPLICATION
TRANSMITTAL**

Attorney Docket No.

210121.475C7

First Inventor or Application Identifier

Steven G. Reed

Title

COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF LUNG CANCER

Express Mail Label No.

EL615232339US

(Only for nonprovisional applications under 37 CFR § 1.53(b))

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO:Box Patent Application
Assistant Commissioner for Patent
Washington, D.C. 202311. ☐ General Authorization Form & Fee Transmittal
(Submit an original and a duplicate for fee processing)2. ☒ Specification [Total Pages] **137**
(preferred arrangement set forth below)

- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention

- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

☐ Drawing(s) (35 USC 113) [Total Sheets]

Oath or Declaration [Total Pages]

a. ☐ Newly executed (original or copy)b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 17 completed)i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting
inventor(s) named in the prior application,
see 37 CFR 1.63(d)(2) and 1.33(b)5. ☐ Incorporation By Reference (useable if box 4b is
checked) The entire disclosure of the prior application,
from which a copy of the oath or declaration is supplied
under Box 4b, is considered to be part of the disclosure of
the accompanying application and is hereby incorporated
by reference therein.6. ☐ Microfiche Computer Program (Appendix)7. Nucleotide and Amino Acid Sequence Submission
(if applicable, all necessary)

- a. ☒ Computer-Readable Copy
- b. ☒ Paper Copy (identical to computer copy)
- c. ☒ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS8. ☐ Assignment Papers (cover sheet & document(s))9. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney10. ☐ English Translation Document (if applicable)11. ☒ Information Disclosure Statement (IDS)/PTO-1449 ☒ Copies of IDS Citations12. ☐ Preliminary Amendment13. ☒ Return Receipt Postcard14. ☐ Small Entity Statement(s) ☐ Statement filed in prior application,
Status still proper and desired15. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)16. ☒ Other: Certificate of Express Mail

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a preliminary amendment

☐ Continuation ☐ Divisional ☒ Continuation-In-Part (CIP) of prior Application No.: **09/640,878**Prior application information: Examiner not assignedGroup / Art Unit not assigned☐ Claims the benefit of Provisional Application No. _____**CORRESPONDENCE ADDRESS**Jane E. R. Potter
Seed Intellectual Property Law Group PLLC
701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900 Fax: (206) 682-6031

Respectfully submitted,

TYPED or PRINTED NAME Jane E. R. PotterSIGNATURE Jane E. R. Potter

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REGISTRATION NO. 33,332Date September 20, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

U.S. PTO
60/234517



Applicants : Steven G. Reed, Bellevue, WA; Michael J. Lodes, Seattle, WA;
Raodoh Mohamath, Seattle, WA; Heather Secrist, Seattle, WA; Darin
R. Benson, Seattle, WA; Carol Yoseph Indirias, Seattle, WA; Robert
A. Henderson, Edmonds, WA; Steven P. Fling, Bainbridge Island,
WA; Paul A. Algate, Issaquah, WA

Filed : September 20, 2000

For : COMPOSITIONS AND METHODS FOR THE THERAPY AND
DIAGNOSIS OF LUNG CANCER

Docket No. : 210121.475C7

Date : September 20, 2000

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Assistant Commissioner for Patents:

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C.F.R. § 1.10, Mailing Label Certificate No. EL615232339US, on September 20, 2000,
addressed to Box Patent Application, Assistant Commissioner for Patents, Washington, DC
20231.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC


Steve Plante/Jeanette West/Susan Johnson

JEP:sds

Enclosures:

- Postcard
- Form PTO/SB/05
- Specification, Claims, Abstract (137 pages)
- Sequence Listing (217 pages)
- Declaration for Sequence Listing
- Diskette for Sequence Listing
- Information Disclosure Statement
- Form PTO-1449
- Cited References (11)

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COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF LUNG CANCER

5 REFERENCE TO RELATED APPLICATIONS

This application is related to U.S. Patent Application No. 09/640,878, filed August 18, 2000; U.S. Patent Application No. 09/588,937, filed May 26, 2000; U.S. Patent Application No. 09/538,037, filed March 29, 2000; U.S. Patent Application No. 09/518,809, filed March 3, 2000; U.S. Patent Application No. 09/476,235 filed December 30, 1999; U.S. Patent Application No. 09/370,838, filed August 9, 1999; and U.S. Patent Application No. 09/285,323, filed April 2, 1999, each a CIP of the previous application and all pending, and PCT/US00/08560, filed March 30, 2000, pending.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as lung cancer. The invention is more specifically related to polypeptides comprising at least a portion of a lung tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in compositions for prevention and treatment of lung cancer, and for the diagnosis and monitoring of such cancers.

20 BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as lung cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a lung tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NOs:217-390, 392, 394, 396, 398-420 and 422-424; (b) variants of a sequence recited in SEQ ID NOs:217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NOs:391, 393, 395, 397, 421, 425-427, 434-439 and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a lung tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, immunogenic
5 compositions, or vaccines for prophylactic or therapeutic use are provided. Such compositions comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a
10 lung tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, immunogenic compositions, or vaccines, are
15 provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding
20 such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Compositions are further provided, within other aspects, that comprise a
25 fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a composition as recited above. The patient may be afflicted with lung cancer, in which case

the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample
5 with T cells that specifically react with a lung tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as
10 described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under
15 conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective
20 amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a lung tumor protein; (ii) a polynucleotide encoding such
25 a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be lung cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an

oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained
 5 from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom
 10 monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

15 These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

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- SEQ ID NO: 102 is the determined DNA sequence for SLT-T1
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 SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93
 SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100
 SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105
 25 SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50
 SEQ ID NO: 217 is the determined cDNA sequence for SSLT-4
 SEQ ID NO: 218 is the determined cDNA sequence for SSLT-9
 SEQ ID NO: 219 is the determined cDNA sequence for SSLT-10
 SEQ ID NO: 220 is the determined cDNA sequence for SSLT-12
 30 SEQ ID NO: 221 is the determined cDNA sequence for SSLT-19

- SEQ ID NO: 222 is the determined cDNA sequence for SSLT-31
 SEQ ID NO: 223 is the determined cDNA sequence for SSLT-38
 SEQ ID NO: 224 is the determined cDNA sequence for LT4690-2
 SEQ ID NO: 225 is the determined cDNA sequence for LT4690-3
 5 SEQ ID NO: 226 is the determined cDNA sequence for LT4690-22
 SEQ ID NO: 227 is the determined cDNA sequence for LT4690-24
 SEQ ID NO: 228 is the determined cDNA sequence for LT4690-37
 SEQ ID NO: 229 is the determined cDNA sequence for LT4690-39
 SEQ ID NO: 230 is the determined cDNA sequence for LT4690-40
 10 SEQ ID NO: 231 is the determined cDNA sequence for LT4690-41
 SEQ ID NO: 232 is the determined cDNA sequence for LT4690-49
 SEQ ID NO: 233 is the determined 3' cDNA sequence for LT4690-55
 SEQ ID NO: 234 is the determined 5' cDNA sequence for LT4690-55
 SEQ ID NO: 235 is the determined cDNA sequence for LT4690-59
 15 SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63
 SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71
 SEQ ID NO: 238 is the determined cDNA sequence for 2LT-3
 SEQ ID NO: 239 is the determined cDNA sequence for 2LT-6
 SEQ ID NO: 240 is the determined cDNA sequence for 2LT-22
 20 SEQ ID NO: 241 is the determined cDNA sequence for 2LT-25
 SEQ ID NO: 242 is the determined cDNA sequence for 2LT-26
 SEQ ID NO: 243 is the determined cDNA sequence for 2LT-31
 SEQ ID NO: 244 is the determined cDNA sequence for 2LT-36
 SEQ ID NO: 245 is the determined cDNA sequence for 2LT-42
 25 SEQ ID NO: 246 is the determined cDNA sequence for 2LT-44
 SEQ ID NO: 247 is the determined cDNA sequence for 2LT-54
 SEQ ID NO: 248 is the determined cDNA sequence for 2LT-55
 SEQ ID NO: 249 is the determined cDNA sequence for 2LT-57
 SEQ ID NO: 250 is the determined cDNA sequence for 2LT-58
 30 SEQ ID NO: 251 is the determined cDNA sequence for 2LT-59

- SEQ ID NO: 252 is the determined cDNA sequence for 2LT-62
 SEQ ID NO: 253 is the determined cDNA sequence for 2LT-63
 SEQ ID NO: 254 is the determined cDNA sequence for 2LT-65
 SEQ ID NO: 255 is the determined cDNA sequence for 2LT-66
 5 SEQ ID NO: 256 is the determined cDNA sequence for 2LT-70
 SEQ ID NO: 257 is the determined cDNA sequence for 2LT-73
 SEQ ID NO: 258 is the determined cDNA sequence for 2LT-74
 SEQ ID NO: 259 is the determined cDNA sequence for 2LT-76
 SEQ ID NO: 260 is the determined cDNA sequence for 2LT-77
 10 SEQ ID NO: 261 is the determined cDNA sequence for 2LT-78
 SEQ ID NO: 262 is the determined cDNA sequence for 2LT-80
 SEQ ID NO: 263 is the determined cDNA sequence for 2LT-85
 SEQ ID NO: 264 is the determined cDNA sequence for 2LT-87
 SEQ ID NO: 265 is the determined cDNA sequence for 2LT-89
 15 SEQ ID NO: 266 is the determined cDNA sequence for 2LT-94
 SEQ ID NO: 267 is the determined cDNA sequence for 2LT-95
 SEQ ID NO: 268 is the determined cDNA sequence for 2LT-98
 SEQ ID NO: 269 is the determined cDNA sequence for 2LT-100
 SEQ ID NO: 270 is the determined cDNA sequence for 2LT-103
 20 SEQ ID NO: 271 is the determined cDNA sequence for 2LT-105
 SEQ ID NO: 272 is the determined cDNA sequence for 2LT-107
 SEQ ID NO: 273 is the determined cDNA sequence for 2LT-108
 SEQ ID NO: 274 is the determined cDNA sequence for 2LT-109
 SEQ ID NO: 275 is the determined cDNA sequence for 2LT-118
 25 SEQ ID NO: 276 is the determined cDNA sequence for 2LT-120
 SEQ ID NO: 277 is the determined cDNA sequence for 2LT-121
 SEQ ID NO: 278 is the determined cDNA sequence for 2LT-122
 SEQ ID NO: 279 is the determined cDNA sequence for 2LT-124
 SEQ ID NO: 280 is the determined cDNA sequence for 2LT-126
 30 SEQ ID NO: 281 is the determined cDNA sequence for 2LT-127

- SEQ ID NO: 282 is the determined cDNA sequence for 2LT-128
 SEQ ID NO: 283 is the determined cDNA sequence for 2LT-129
 SEQ ID NO: 284 is the determined cDNA sequence for 2LT-133
 SEQ ID NO: 285 is the determined cDNA sequence for 2LT-137
 5 SEQ ID NO: 286 is the determined cDNA sequence for LT4690-71
 SEQ ID NO: 287 is the determined cDNA sequence for LT4690-82
 SEQ ID NO: 288 is the determined full-length cDNA sequence for SSLT-74
 SEQ ID NO: 289 is the determined cDNA sequence for SSLT-78
 SEQ ID NO: 290 is the determined cDNA sequence for SCC1-8.
 10 SEQ ID NO: 291 is the determined cDNA sequence for SCC1-12.
 SEQ ID NO: 292 is the determined cDNA sequence for SCC1-336
 SEQ ID NO: 293 is the determined cDNA sequence for SCC1-344
 SEQ ID NO: 294 is the determined cDNA sequence for SCC1-345
 SEQ ID NO: 295 is the determined cDNA sequence for SCC1-346
 15 SEQ ID NO: 296 is the determined cDNA sequence for SCC1-348
 SEQ ID NO: 297 is the determined cDNA sequence for SCC1-350
 SEQ ID NO: 298 is the determined cDNA sequence for SCC1-352
 SEQ ID NO: 299 is the determined cDNA sequence for SCC1-354
 SEQ ID NO: 300 is the determined cDNA sequence for SCC1-355
 20 SEQ ID NO: 301 is the determined cDNA sequence for SCC1-356
 SEQ ID NO: 302 is the determined cDNA sequence for SCC1-357
 SEQ ID NO: 303 is the determined cDNA sequence for SCC1-501
 SEQ ID NO: 304 is the determined cDNA sequence for SCC1-503
 SEQ ID NO: 305 is the determined cDNA sequence for SCC1-513
 25 SEQ ID NO: 306 is the determined cDNA sequence for SCC1-516
 SEQ ID NO: 307 is the determined cDNA sequence for SCC1-518
 SEQ ID NO: 308 is the determined cDNA sequence for SCC1-519
 SEQ ID NO: 309 is the determined cDNA sequence for SCC1-522
 SEQ ID NO: 310 is the determined cDNA sequence for SCC1-523
 30 SEQ ID NO: 311 is the determined cDNA sequence for SCC1-525

- SEQ ID NO: 312 is the determined cDNA sequence for SCC1-527
 SEQ ID NO: 313 is the determined cDNA sequence for SCC1-529
 SEQ ID NO: 314 is the determined cDNA sequence for SCC1-530
 SEQ ID NO: 315 is the determined cDNA sequence for SCC1-531
 5 SEQ ID NO: 316 is the determined cDNA sequence for SCC1-532
 SEQ ID NO: 317 is the determined cDNA sequence for SCC1-533
 SEQ ID NO: 318 is the determined cDNA sequence for SCC1-536
 SEQ ID NO: 319 is the determined cDNA sequence for SCC1-538
 SEQ ID NO: 320 is the determined cDNA sequence for SCC1-539
 10 SEQ ID NO: 321 is the determined cDNA sequence for SCC1-541
 SEQ ID NO: 322 is the determined cDNA sequence for SCC1-542
 SEQ ID NO: 323 is the determined cDNA sequence for SCC1-546
 SEQ ID NO: 324 is the determined cDNA sequence for SCC1-549
 SEQ ID NO: 325 is the determined cDNA sequence for SCC1-551
 15 SEQ ID NO: 326 is the determined cDNA sequence for SCC1-552
 SEQ ID NO: 327 is the determined cDNA sequence for SCC1-554
 SEQ ID NO: 328 is the determined cDNA sequence for SCC1-558
 SEQ ID NO: 329 is the determined cDNA sequence for SCC1-559
 SEQ ID NO: 330 is the determined cDNA sequence for SCC1-561
 20 SEQ ID NO: 331 is the determined cDNA sequence for SCC1-562
 SEQ ID NO: 332 is the determined cDNA sequence for SCC1-564
 SEQ ID NO: 333 is the determined cDNA sequence for SCC1-565
 SEQ ID NO: 334 is the determined cDNA sequence for SCC1-566
 SEQ ID NO: 335 is the determined cDNA sequence for SCC1-567
 25 SEQ ID NO: 336 is the determined cDNA sequence for SCC1-568
 SEQ ID NO: 337 is the determined cDNA sequence for SCC1-570
 SEQ ID NO: 338 is the determined cDNA sequence for SCC1-572
 SEQ ID NO: 339 is the determined cDNA sequence for SCC1-575
 SEQ ID NO: 340 is the determined cDNA sequence for SCC1-576
 30 SEQ ID NO: 341 is the determined cDNA sequence for SCC1-577

- SEQ ID NO: 342 is the determined cDNA sequence for SCC1-578
 SEQ ID NO: 343 is the determined cDNA sequence for SCC1-582
 SEQ ID NO: 344 is the determined cDNA sequence for SCC1-583
 SEQ ID NO: 345 is the determined cDNA sequence for SCC1-586
 5 SEQ ID NO: 346 is the determined cDNA sequence for SCC1-588
 SEQ ID NO: 347 is the determined cDNA sequence for SCC1-590
 SEQ ID NO: 348 is the determined cDNA sequence for SCC1-591
 SEQ ID NO: 349 is the determined cDNA sequence for SCC1-592
 SEQ ID NO: 350 is the determined cDNA sequence for SCC1-593
 10 SEQ ID NO: 351 is the determined cDNA sequence for SCC1-594
 SEQ ID NO: 352 is the determined cDNA sequence for SCC1-595
 SEQ ID NO: 353 is the determined cDNA sequence for SCC1-596
 SEQ ID NO: 354 is the determined cDNA sequence for SCC1-598
 SEQ ID NO: 355 is the determined cDNA sequence for SCC1-599
 15 SEQ ID NO: 356 is the determined cDNA sequence for SCC1-602
 SEQ ID NO: 357 is the determined cDNA sequence for SCC1-604
 SEQ ID NO: 358 is the determined cDNA sequence for SCC1-605
 SEQ ID NO: 359 is the determined cDNA sequence for SCC1-606
 SEQ ID NO: 360 is the determined cDNA sequence for SCC1-607
 20 SEQ ID NO: 361 is the determined cDNA sequence for SCC1-608
 SEQ ID NO: 362 is the determined cDNA sequence for SCC1-610
 SEQ ID NO: 363 is the determined cDNA sequence for clone DMS79T1
 SEQ ID NO: 364 is the determined cDNA sequence for clone DMS79T2
 SEQ ID NO: 365 is the determined cDNA sequence for clone DMS79T3
 25 SEQ ID NO: 366 is the determined cDNA sequence for clone DMS79T5
 SEQ ID NO: 367 is the determined cDNA sequence for clone DMS79T6
 SEQ ID NO: 368 is the determined cDNA sequence for clone DMS79T7
 SEQ ID NO: 369 is the determined cDNA sequence for clone DMS79T9
 SEQ ID NO: 370 is the determined cDNA sequence for clone DMS79T10
 30 SEQ ID NO: 371 is the determined cDNA sequence for clone DMS79T11

- SEQ ID NO: 372 is the determined cDNA sequence for clone 128T1
 SEQ ID NO: 373 is the determined cDNA sequence for clone 128T2
 SEQ ID NO: 374 is the determined cDNA sequence for clone 128T3
 SEQ ID NO: 375 is the determined cDNA sequence for clone 128T4
 5 SEQ ID NO: 376 is the determined cDNA sequence for clone 128T5
 SEQ ID NO: 377 is the determined cDNA sequence for clone 128T7
 SEQ ID NO: 378 is the determined cDNA sequence for clone 128T9
 SEQ ID NO: 379 is the determined cDNA sequence for clone 128T10
 SEQ ID NO: 380 is the determined cDNA sequence for clone 128T11
 10 SEQ ID NO: 381 is the determined cDNA sequence for clone 128T12
 SEQ ID NO: 382 is the determined cDNA sequence for clone NCIH69T3
 SEQ ID NO: 383 is the determined cDNA sequence for clone NCIH69T5
 SEQ ID NO: 384 is the determined cDNA sequence for clone NCIH69T6
 SEQ ID NO: 385 is the determined cDNA sequence for clone NCIH69T7
 15 SEQ ID NO: 386 is the determined cDNA sequence for clone NCIH69T9
 SEQ ID NO: 387 is the determined cDNA sequence for clone NCIH69T10
 SEQ ID NO: 388 is the determined cDNA sequence for clone NCIH69T11
 SEQ ID NO: 389 is the determined cDNA sequence for clone NCIH69T12
 SEQ ID NO: 390 is the full-length cDNA sequence for 128T1
 20 SEQ ID NO: 391 is the amino acid sequence for 128T1
 SEQ ID NO: 392 is the full-length cDNA sequence for 2LT-128
 SEQ ID NO: 393 is the amino acid sequence for 2LT-128
 SEQ ID NO: 394 is an extended cDNA sequence for clone SCC1-542
 SEQ ID NO: 395 is the amino acid sequence corresponding to SEQ ID NO:394
 25 SEQ ID NO: 396 is an extended cDNA sequence for clone SCC1-593
 SEQ ID NO: 397 is the amino acid sequence corresponding to SEQ ID NO:396
 SEQ ID NO:398 is the determined cDNA sequence for 55508.1
 SEQ ID NO:399 is the determined cDNA sequence for 55509.1
 SEQ ID NO:400 is the determined cDNA sequence for 54243.1
 30 SEQ ID NO:401 is the determined cDNA sequence for 54251.1

- SEQ ID NO:402 is the determined cDNA sequence for 54252.1
 SEQ ID NO:403 is the determined cDNA sequence for 54253.1
 SEQ ID NO:404 is the determined cDNA sequence for 55518.1
 SEQ ID NO:405 is the determined cDNA sequence for 54258.1
 5 SEQ ID NO:406 is the determined cDNA sequence for 54575.1
 SEQ ID NO:407 is the determined cDNA sequence for 54577.1
 SEQ ID NO:408 is the determined cDNA sequence for 54584.1
 SEQ ID NO:409 is the determined cDNA sequence for 55521.1
 SEQ ID NO:410 is the determined cDNA sequence for 54589.1
 10 SEQ ID NO:411 is the determined cDNA sequence for 54592.1
 SEQ ID NO:412 is the determined cDNA sequence for 55134.1
 SEQ ID NO:413 is the determined cDNA sequence for 55137.1
 SEQ ID NO:414 is the determined cDNA sequence for 55140.1
 SEQ ID NO:415 is the determined cDNA sequence for 55531.1
 15 SEQ ID NO:416 is the determined cDNA sequence for 55532.1
 SEQ ID NO:417 is the determined cDNA sequence for 54621.1
 SEQ ID NO:418 is the determined cDNA sequence for 55548.1
 SEQ ID NO:419 is the determined cDNA sequence for 54623.1
 SEQ ID NO:420 is the determined cDNA sequence for L39
 20 SEQ ID NO:421 is the predicted amino acid sequence for L39
 SEQ ID NO:422 is the determined cDNA sequence for SCC2-29
 SEQ ID NO:423 is the determined cDNA sequence for SCC2-36
 SEQ ID NO:424 is the determined cDNA sequence for SCC2-60
 SEQ ID NO:425 is the predicted amino acid sequence for SCC2-29
 25 SEQ ID NO:426 is the predicted amino acid sequence for SCC2-36
 SEQ ID NO:427 is the predicted amino acid sequence for SCC2-60
 SEQ ID NO:428 is an extended cDNA sequence for the clone 20129, also referred to as
 2LT-3, set forth in SEQ ID NO: 238
 SEQ ID NO:429 is an extended cDNA sequence for the clone 20347, also referred to as
 30 2LT-26, set forth in SEQ ID NO: 242

SEQ ID NO:430 is an extended cDNA sequence for the clone 21282, also referred to as 2LT-57, set forth in SEQ ID NO: 249

SEQ ID NO:431 is an extended cDNA sequence for the clone 21283, also referred to as 2LT-58, set forth in SEQ ID NO: 250

5 SEQ ID NO:432 is an extended cDNA sequence for the clone 21484, also referred to as 2LT-98, set forth in SEQ ID NO: 268

SEQ ID NO:433 is an extended cDNA sequence for the clone 21871, also referred to as 2LT-124, set forth in SEQ ID NO: 279

SEQ ID NO:434 is an amino acid sequence encoded by SEQ ID NO: 428

10 SEQ ID NO:435 is an amino acid sequence encoded by SEQ ID NO: 429

SEQ ID NO:436 is an amino acid sequence encoded by SEQ ID NO: 430

SEQ ID NO:437 is an amino acid sequence encoded by SEQ ID NO: 431

SEQ ID NO:438 is an amino acid sequence encoded by SEQ ID NO: 432

SEQ ID NO:439 is an amino acid sequence encoded by SEQ ID NO: 433

15 SEQ ID NO:440 is the determined cDNA sequence for clone 19A4

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as lung cancer. Certain illustrative compositions described herein include lung tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). A "lung tumor protein," as the term is used herein, refers generally to a protein that is expressed in lung tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain lung tumor proteins are tumor proteins that

react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with lung cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NOs:217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NOs:391, 393, 395 and 397, 421, 425-427 and 434-439, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human lung cancer.

10 POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally

isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a lung tumor protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term “variants” also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be “identical” if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A “comparison window” as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment

schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenesis pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score.

Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

10 Preferably, the “percentage of sequence identity” is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which
15 does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by
20 100 to yield the percentage of sequence identity.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence
25 identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide

sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a

solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as
 5 a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided
 10 herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

15 PROBES AND PRIMERS

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same
 20 sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

25 The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned,

such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NOs:217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be

readily manipulated, and thus will generally be a method of choice depending on the desired results.

POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any
 5 of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to
 10 the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as lung tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this
 15 approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a lung tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is
 20 screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by
 25 nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor

Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then be assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia *et al.*, *Nucl. Acids Res.* 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector

sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom *et al.*, *PCR Methods Applic.* 1:111-19, 1991) and walking PCR (Parker *et al.*, *Nucl. Acids. Res.* 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

5 In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be
10 obtained by analysis of genomic fragments.

POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

 In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct
15 expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

 As will be understood by those of skill in the art, it may be advantageous in
20 some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

25 Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA

shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSFORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to

generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of β -galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J.* 3:1671-1680;

Broglie, R. *et al.* (1984) *Science* 224:838-843; and Winter, J. *et al.* (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. *et al.* (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate

expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. *et al.* (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. *et al.* (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. *et al.* (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. *et al.* (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. *et al.* (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations

and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med.* 158:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may

be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such

5 purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or

10 enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal

15 ion affinity chromatography) as described in Porath, J. *et al.* (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. *et al.* (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the

20 invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and

25 combined using chemical methods to produce the full length molecule.

SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific

mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific
5 mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve,
10 alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties
15 of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in
20 length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors
25 such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is
 5 prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to
 10 transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants
 15 of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kubby, 1994; and Maniatis *et al.*, 1982, each incorporated herein
 20 by reference, for that purpose.

As used herein, the term “oligonucleotide directed mutagenesis procedure” refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as
 25 amplification. As used herein, the term “oligonucleotide directed mutagenesis procedure” is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example,

Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in
5 its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S.
10 Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the
15 primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification
20 procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the
25 presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR™, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S.

Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α -thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is

repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is
 5 incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (*e.g.*, biotin) and/or a detector moiety (*e.g.*, enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the
 10 probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh *et al.*, 1989; PCT Intl. Pat. Appl. Publ. No. WO
 15 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve
 20 annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a
 25 polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing

single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of
 5 ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a
 10 double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done
 15 isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA")
 20 followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence
 25 of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU			
Cysteine	Cys	C	UGC	UGU					
Aspartic acid	Asp	D	GAC	GAU					
Glutamic acid	Glu	E	GAA	GAG					
Phenylalanine	Phe	F	UUC	UUU					
Glycine	Gly	G	GGA	GGC	GGG	GGU			
Histidine	His	H	CAC	CAU					
Isoleucine	Ile	I	AUA	AUC	AUU				
Lysine	Lys	K	AAA	AAG					
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU	
Methionine	Met	M	AUG						
Asparagine	Asn	N	AAC	AAU					
Proline	Pro	P	CCA	CCC	CCG	CCU			
Glutamine	Gln	Q	CAA	CAG					
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU	
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU	
Threonine	Thr	T	ACA	ACC	ACG	ACU			
Valine	Val	V	GUA	GUC	GUG	GUU			
Tryptophan	Trp	W	UGG						
Tyrosine	Tyr	Y	UAC	UAU					

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive
5 biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been

assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 \pm 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their

hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

5 In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other
10 modified forms of adenine, cytidine, guanine, thymine and uridine.

IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

 In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety of well known approaches, several of which are outlined below for
15 the purpose of illustration.

1. ADENOVIRUS

 One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences
20 sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

 The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-
25 stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because

adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease
 5 such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The
 10 early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication,
 15 late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence
 20 which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual
 25 plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is

dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup
 5 C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is
 10 replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted
 15 E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, *e.g.*, 10^9 - 10^{11} plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not
 20 require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch *et al.*, 1963; Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

25 Adenovirus vectors have been used in eukaryotic gene expression (Levrero *et al.*, 1991; Gomez-Foix *et al.*, 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet *et al.*, 1990; Rich *et al.*, 1993). Studies in administering recombinant

adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993), peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

5 2. RETROVIRUSES

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results
 10 in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome.
 15 These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order
 20 to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be
 25 packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene

transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzyczka, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral

promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector. One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive

properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang *et al.*, 1991).

5. NON-VIRAL VECTORS

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell

membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e.* *ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for

polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism
 5 to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense
 10 inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense
 15 constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides
 20 oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a
 25 phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m , binding energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

RIBOZYMES

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et*

al., 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

5 Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*, 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus,
10 sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-*ras*, c-*fos* and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon
15 that is cleaved by a specific ribozyme.

 Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through
20 the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an
25 encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

 The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to

a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the
 5 ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action
 10 of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are
 15 described by Rossi *et al.* (1992). Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel *et al.* (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada *et al.* (1983); Neurospora VS RNA
 20 ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it
 25 have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as

one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific
 5 cells.

Small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells
 10 from eukaryotic promoters (*e.g.*, Scanlon *et al.*, 1991; Kashani-Sabet *et al.*, 1992; Dropulic *et al.*, 1992; Weerasinghe *et al.*, 1991; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Sarver *et al.*, 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No.
 15 WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa *et al.*, 1992; Taira *et al.*, 1991; and Ventura *et al.*, 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo*
 20 through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such
 25 ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger *et al.*, 1989) to assess whether the ribozyme sequences fold into

the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-o-methyl, 2'-H (for a review see *e.g.*, Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al.*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be

administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber *et al.*, 1993; Zhou *et al.*, 1990). Ribozymes expressed from such promoters can function in mammalian cells (*e.g.* Kashani-Saber *et al.*, 1992; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Yu *et al.*, 1993; L'Huillier *et al.*, 1992; Lisiewicz *et al.*, 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational therapies (*e.g.*, multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter,

decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific

functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaima *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; Griffith *et al.*, 1995; Kremsky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

10 In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

15 Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of T_m on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence

specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a
 5 single mismatch within a 16 bp PNA-DNA duplex can reduce the T_m by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

10 High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and
 15 this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will occur
 20 spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene
 25 expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by
 5 Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen *et al.*, 1991), antisense inhibition (Hanvey *et al.*, 1992), mutational analysis (Orum *et al.*, 1993), enhancers of transcription (Mollegaard *et al.*, 1994), nucleic acid purification (Orum *et al.*, 1995), isolation of transcriptionally active genes (Boffa *et al.*, 1995), blocking of
 10 transcription factor binding (Vickers *et al.*, 1995), genome cleavage (Veselkov *et al.*, 1996), biosensors (Wang *et al.*, 1996), *in situ* hybridization (Thisted *et al.*, 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

The present invention, in other aspects, provides polypeptide compositions.
 15 Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a
 20 contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the
 25 amino acid sequence disclosed in SEQ ID NO: 391 and 393, or to active fragments, or to variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are

immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO: 217-390 and 392, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

5 Particularly illustrative polypeptides include the amino acid sequence disclosed in SEQ ID NO:391, 393, 395, 397, 421 and 425-427.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially
10 the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a lung tumor protein or a variant thereof, as described herein. As noted above, a "lung tumor protein" is a protein that is expressed by lung tumor cells. Proteins that are lung tumor proteins also react detectably within an
15 immunoassay (such as an ELISA) with antisera from a patient with lung cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is
20 recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a lung tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been
25 deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247

(Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native lung tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native lung tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native lung tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30

amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
 5 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the
 10 secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids
 15 with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or
 20 alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

25 As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-

His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above
 5 may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant
 10 cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally,
 15 one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides
 20 may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may
 25 be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological

fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene* 40:39-46, 1985; Murphy *et al.*, *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may

generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see, for example, Stoute et al. New Engl. J. Med.*, 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-

terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10:795-798, 1992*). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a lung tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a lung tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a lung tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex

formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a lung tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as

bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, 5 *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, 10 differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, Shigella toxin, and pokeweed 15 antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or 20 sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an 25 antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter *et al.*), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn *et al.*), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler *et al.*).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato *et al.*), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih *et al.*). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide

agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison *et al.* discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a lung tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a lung tumor polypeptide, polynucleotide encoding a lung tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a lung tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a lung tumor polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the

polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen *et al.*, *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a lung tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan *et al.*, Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a lung tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Lung tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a lung tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a lung tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a lung tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a lung tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz *et al.*, 1997; Hwang *et al.*, 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing,

for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of
5 surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying
10 absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In
15 this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will
20 necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

25 Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other

ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

5 The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived
10 from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable
15 solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art.
20 Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when
25 administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran *et al.*, 1997; Margalit, 1995;

U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trails examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)). MLVs generally have diameters of from 25 nm to 4 μ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drug-bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is

disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be

used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable
 5 nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-
 10 cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be easily made, as described (Couvreur *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

IMMUNOGENIC COMPOSITIONS

15 In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an
 20 exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical
 25 compositions and immunogenic compositions within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch *et al.*, *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner *et al.*, *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner *et al.*, *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld *et al.*, *Science* 252:431-434, 1991; Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler *et al.*, *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman *et al.*, *Circulation* 88:2838-2848, 1993; and Guzman *et al.*, *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer *et al.*, *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may provide for an enhanced immune response.

It will be apparent that an immunogenic composition may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively,

compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included.

5 Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and
10 Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -
15 12, may also be used as adjuvants.

Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN- γ , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In
20 contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent
25 than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-

acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; *see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response.

- 5 Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato *et al.*, *Science* 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For
- 10 example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-
- 15 MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and

20 other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a

25 suitable carrier or excipient. The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see, e.g.*, Coombes *et al.*, *Vaccine* 14:1429-1438, 1996) and administered by,

for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

5 Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a
10 cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the
15 condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes
20 and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs,
25 including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be

effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within an immunogenic composition (*see* Zitvogel *et al.*, *Nature Med.* 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF α to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF α , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc γ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion

molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a lung tumor protein (or portion or other variant thereof) such that the lung tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi *et al.*, *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the lung tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a immunogenic composition or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as lung cancer. Within such methods, pharmaceutical compositions and immunogenic compositions are typically administered to a patient. As used herein, a “patient” refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and immunogenic compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and immunogenic compositions may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other

vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever *et al.*, *Immunological Reviews* 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions

and immunogenic compositions may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such immunogenic compositions should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in treated patients as compared to non-treated patients. In general, for pharmaceutical compositions and immunogenic compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a lung tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the

labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and portions thereof to which the binding agent binds, as described above.

5 The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic
10 particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which
15 may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1
20 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

 Covalent attachment of binding agent to a solid support may generally be
25 achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group

on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound
 5 detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group
 10 (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally
 15 compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate
 20 preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett *et al.*, *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value
 25 for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the

false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use lung tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample.

The detection of such lung tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a lung tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a lung tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of lung tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a lung tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a lung tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the lung tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a lung tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a lung tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NOs:217-390, 392, 394, 396, 398-420 and 422-424. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed

as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

5 Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

10 As noted above, to improve sensitivity, multiple lung tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in
15 optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

 The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for
20 performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a lung tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or
25 buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a lung tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a lung tumor protein. Such an oligonucleotide may be used, for example, within
5 a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a lung tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

10

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Example 1

PREPARATION OF LUNG TUMOR-SPECIFIC CDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

5 This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

 Tissue samples were prepared from lung tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was
10 isolated and converted into cDNA using a (dT)₁₂AG (SEQ ID NO: 47) anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM MgCl₂, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30
15 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

 Comparison of these sequences to those in the public databases using the
20 BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

Example 2USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING
LUNG TUMOR ANTIGENS

5

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed
10 employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A⁺ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was screened using *E. coli*-absorbed autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A*
15 *Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

20 Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 are provided in SEQ ID NO: 17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO: 25, with the
25 corresponding predicted amino acid sequences from the 3' and 5' ends being provided in SEQ ID NO: 40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6,

LT86-8, LT86-11, LT86-12 and LT86-15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcription regulation mediator. Clone LT86-13 was found to show some
 5 homology with a *C. elegans* leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions
 10 in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

15 Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for
 20 LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

25 In further studies, a cDNA expression library was prepared using mRNA from a lung small cell carcinoma cell line in the lambda ZAP Express expression vector (Stratagene), and screened as described above, with a pool of two lung small cell carcinoma patient sera. The sera pool was adsorbed with *E. coli* lysate and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue.

Seventy-three clones were isolated. The determined cDNA sequences of these clones are provided in SEQ ID NO: 290-362. The sequences of SEQ ID NO: 289-292, 294, 296-297, 300, 302, 303, 305, 307-315, 317-320, 322-325, 327-332, 334, 335, 338-341, 343-352, 354-358, 360 and 362 were found to show some homology to previously isolated genes.

5 The sequences of SEQ ID NO: 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 were found to show some homology to previously identified ESTs.

Example 3

10 USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as

15 described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL

20 Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are

25 provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described

above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-83.

Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A⁺ RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO:

139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology to previously identified human polynucleotide sequences.

Example 4

5 USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

 This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with
10 mouse anti-tumor sera.

 A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A⁺ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice
15 implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage was purified and
20 phagemid excised for 100 clones with insert in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

 The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182,
25 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 187 and 216.

Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences
 5 of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

Using the procedures described above, two directional cDNA libraries
 10 (referred to as LT46-90 and LT86-21) were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237 and 286-289. SEQ ID NO: 286 was found to be a longer sequence of LT4690-71 (SEQ ID NO: 237). Comparison of
 15 these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO: 219, 220, 225, 226, 287 and 288. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to a known mouse mRNA sequence. The sequences of SEQ ID NO: 217, 223,
 20 227-237, 286 and 289 showed some homology to known human DNA and/or RNA sequences.

In further studies using the techniques described above, one of the cDNA libraries described above (LT86-21) was screened with *E. coli*-absorbed mouse anti-SCID tumor serum. This serum was obtained from normal mice immunized with a pool of 3 sera taken from SCID mice implanted with human squamous lung carcinomas. The determined
 5 cDNA sequences for the isolated clones are provided in SEQ ID NO: 238-285. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 253, 260, 277 and 285. The sequences of SEQ ID NO: 249, 250, 256, 266, 276 and 282 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 238-248, 251, 252, 254,
 10 255, 257-259, 261-263, 265, 267-275, 278-281, 283 and 284 were found to show some homology to previously identified DNA or RNA sequences.

Full-length sequencing studies on antigen 2LT-128 (SEQ ID NO: 282) resulted in the isolation of the full-length cDNA sequence provided in SEQ ID NO: 392. This amino acid sequence encoded by this full-length cDNA sequence is provided in SEQ
 15 ID NO: 393. This antigen shows 20-fold over-expression in squamous cell carcinoma and 2.5-fold over-expression in lung adenocarcinoma. This gene has been described as a potential ras oncogene (Fenwick et al. *Science*, 287:869-873, 2000).

Extended sequence information was obtained for clones 2LT-3 (SEQ ID NO:238), 2LT-26 (SEQ ID NO:242), 2LT-57 (SEQ ID NO: 249), 2LT-58 (SEQ ID
 20 NO:250), 2LT-98 (SEQ ID NO:268) and 2LT-124 (SEQ ID NO:279). The extended cDNA sequences for these clones are set forth in SEQ ID NOs:428-433, respectively, encoding the polypeptide sequences set forth in SEQ ID NOs: 434-439, respectively.

Example 5

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2 µg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 µl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor, colon tumor and lung tumor), and different normal tissues, including lung from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A⁺ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol.* 9:79-87; Okamoto, K. et al. 1996 *Int. J. Cancer* 65:437-41; Wu, C. et al. 1995 *Biochem. Biophys. Res. Commun.* 214:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxicol.* 9:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A⁺ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

cDNA sequences encoding antigens potentially involved in small cell lung carcinoma development were isolated as follows. cDNA expression libraries were constructed with mRNA from the small cell lung carcinoma cell lines NCIH69, NCIH128 and DMS79 (all available from the American Type Culture Collection, Manassas, VA) employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Phagemid were rescued at random and the cDNA sequences of 27 isolated clones were determined. Comparison of the determined cDNA sequences revealed no significant homologies to the sequences of SEQ ID NO: 372 and 373. The sequences of SEQ ID NO: 364, 369, 377, 379 and 386 showed some homology to previously isolated ESTs. The sequences of the remaining 20 clones showed some homology to previously identified genes. The cDNA sequences of these clones are provided in SEQ ID NO: 363, 365-368, 370, 371, 374-376, 378, 380-385 and 387-389, wherein SEQ ID NO: 363, 366-368, 370, 375, 376, 378, 380-382, 384 and 385 are full-length sequences.

Comparison of the cDNA sequence of SEQ ID NO: 372 indicated that this clone (referred to as 128T1) is a novel member of a family of putative seven pass transmembrane proteins. Specifically, using the computer algorithm PSORT, the protein was predicted to be a type IIIA plasma membrane seven pass transmembrane protein. A genomic clone was identified in the Genbank database which contained the predicted N-terminal 58 amino acids missing from the amino acid sequence encoded by SEQ ID NO: 372. The determined full-length cDNA sequence for the 128T1 clone is provided in SEQ ID NO: 390, with the corresponding amino acid sequence being provided in SEQ ID NO: 391.

Example 7

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

Example 8ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING LUNG
TUMOR ANTIGENS BY T-CELL EXPRESSION CLONING

5

Lung tumor antigens may also be identified by T cell expression cloning. One source of tumor specific T cells is from surgically excised tumors from human patients.

A non-small cell lung carcinoma was minced and enzymatically digested for
10 several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands were harvested from the interfaces; the upper band at the
15 75%/HBSS interface contained predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contained a majority of lymphocytes. The TILs were expanded in culture, either in 24-well plates with culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively, 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibody OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a high percentage were CD8⁺ T cells (>90% of gated population) with only a
20 small percentage of CD4⁺ cells.

In addition, non-small cell lung carcinoma cells were expanded in culture using standard techniques to establish a tumor cell line, which was later confirmed to be a lung carcinoma cell line by immunohistochemical analysis. This tumor cell line was transduced with a retroviral vector to express human CD80, and characterized by FACS
25 analysis to confirm high expression levels of CD80, class I MHC and class II MHC molecules.

The ability of the TIL lines to specifically recognize autologous lung tumor was demonstrated by cytokine release assays (IFN- γ and TNF- α) as well as ⁵¹Cr release assays. Briefly, TIL cells from day 21 cultures were co-cultured with either autologous or

allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562, and the culture supernatant monitored by ELISA for the presence of cytokines. The TIL specifically recognized autologous tumor but not allogeneic tumor. In addition, there was no recognition of EBV-immortalized LCL or the control cell lines, indicating that the TIL lines are tumor specific and are potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitable numbers for T cell expression cloning using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-2.

Clones from the expanded TIL lines were generated by standard limiting dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. The specificity of these clones for autologous tumor was confirmed by ^{51}Cr microcytotoxicity and IFN- γ bioassays.

These CTL clones were demonstrated to be HLA-B/C restricted by antibody blocking experiments. A representative CTL clone was tested on a panel of allogeneic lung carcinomas and it recognized both autologous tumor and a lung squamous cell carcinoma (936T). As the only class I MHC molecule shared among these tumors was HLA-Cw1203, this indicated that this was the restriction element used by the CTL. This finding was confirmed by the recognition of a number of allogeneic lung carcinomas transduced with a retroviral vector encoding HLA-Cw1203 by the CTL.

PolyA mRNA was prepared from lung tumor LT391-06 cells using Message Maker (Life Technologies; Rockville, MD). The subsequent steps involving cDNA synthesis were performed according to Life Technologies cloning manual (SuperScript Plasmid System for cDNA Synthesis and Plasmid Cloning). Modifications to the protocol were made as follows. At the adapter addition step, EcoRI-XmnI adapters (d(AATTCGAACCCCTTCG), New England Biolabs; Beverly, MA) were substituted. Size fractionated cDNAs were ligated into the expression vector system HisMax A, B, C

(Invitrogen; Carlsbad, CA) to optimize for protein expression in all three coding frames. Library plasmids were then aliquotted at approximately 100 CFU/well into a 96-well block for overnight liquid amplification. From these cultures, glycerols stocks were made and pooled plasmid was prepared by auotmated robot (Qiagen; Valencia, CA). The
 5 concentration of the plasmid DNA in each well of the library plates was determined to be approximately 150 ng/ul. For T cell screening, approximately 80 ng of the library plasmid DNA and 80 ng of HLA-Cw1203 plasmid DNA was mixed with the lipid Eugene according the the manufacturers instructions and transfected in duplicate into COS-7 cells. After incubation at 37 C for 48 hours, the transfection mixture was removed and 10,000
 10 LT391-06 CTL were added to each well in fresh media containing human serum.

The ability of the T cells to recognize an antigen in the library was assessed by cytokine release after 6 hours (TNF-alpha, WEHI bio-assay) or after 24 hours (IFN-gamma, ELISA). Approximately $\sim 2.0 \times 10^5$ clones (in plasmid pools of 100) have been screened using this system in COS-7 cells. Three plasmid pools were identified (14F10,
 15 19A4, and 20E10) that were recognized by LT391-06 CTL. Transfection of these plasmid pools into COS-7 cells led to production of both IFN-gamma and TNF-alpha from the LT391-06 CTL significantly above background. Pools 14F10 and 19A4 were "broken down" into several hundred individual plasmid DNAs and retested. One plasmid (3D9) from pool 14F10 and 5 plasmids (2A6, 2E11, 2F12, 3F4, 3H8) from 19A4 pool were
 20 capable of reconstituting T cell recognition.

The sequencing of these plasmids identified a 7.8 kB cDNA insert (clone 14F10) and also a 2.2 kB cDNA insert (clone 19A4; SEQ ID NO:440). Clone 19A4 is contained within the 5' region of clone 14F10. BLAST search analysis against the GenBank database identified both of these sequences as having significant homology with
 25 a truncated human cystine/glutamate transporter gene. Unlike the published sequence, however, clones 14F10 and 19A4 contained a unique 5' terminus consisting of 181 nucleotides. This novel sequence replaces the published 5' region and results in the removal of the reported initiating methionine (start codon) and an additional two amino acids of the reported transporter protein. Therefore, the translated product of clones 14F10 and 19A4 is

From the foregoing it will be appreciated that, although specific
5 embodiments of the invention have been described herein for purposes of illustration,
various modifications may be made without deviating from the spirit and scope of the
invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is claimed:

1. An isolated polypeptide, comprising at least an immunogenic portion of a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
 - (a) sequences recited in SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440;
 - (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 under moderately stringent conditions; and
 - (c) complements of sequences of (a) or (b).
2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 or a complement of any of the foregoing polynucleotide sequences.
3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 391, 393, 395, 397, 421 and 425-427.
4. An isolated polynucleotide encoding at least 15 amino acid residues of a lung tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid

sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440, or a complement of any of the foregoing sequences.

5. An isolated polynucleotide encoding a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 or a complement of any of the foregoing sequences.

6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440.

7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 under moderately stringent conditions.

8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.

9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.

10. A host cell transformed or transfected with an expression vector according to claim 9.

11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a lung tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 or a complement of any of the foregoing polynucleotide sequences.

12. A fusion protein, comprising at least one polypeptide according to claim 1.

13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.

16. An isolated polynucleotide encoding a fusion protein according to claim 12.

17. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

- (a) a polypeptide according to claim 1;
- (b) a polynucleotide according to claim 4;

- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.

18. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:

- (a) a polypeptide according to claim 1;
- (b) a polynucleotide according to claim 4;
- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.

19. An immunogenic composition according to claim 18, wherein the immunostimulant is an adjuvant.

20. An immunogenic composition according to claim 18, wherein the immunostimulant induces a predominantly Type I response.

21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.

22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 18.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.

25. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);
in combination with an immunostimulant.

26. An immunogenic composition according to claim 25, wherein the immunostimulant is an adjuvant.

27. An immunogenic composition according to claim 25, wherein the immunostimulant induces a predominantly Type I response.

28. An immunogenic composition according to claim 25, wherein the antigen-presenting cell is a dendritic cell.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);

and thereby inhibiting the development of a cancer in the patient.

30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.

31. A method according to any one of claims 21, 22 and 29, wherein the cancer is lung cancer.

32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.

34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 32.

35. A method for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) sequences recited in SEQ ID NOs: 217-390, 392, 396, 398-420, 422-424, 428-433 and 440;

(ii) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-390, 392, 396, 398-420, 422-424, 428-433 and 440 under moderately stringent conditions; and

(iii) complements of sequences of (i) or (ii);

(b) polynucleotides encoding a polypeptide of (a); and

(c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.

37. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 217-

390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

38. A method according to claim 37, wherein the binding agent is an antibody.

39. A method according to claim 38, wherein the antibody is a monoclonal antibody.

COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF LUNG CANCER

ABSTRACT OF THE DISCLOSURE

Compositions and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Compositions may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Steven G. Reed et al.
Filed : September 20, 2000
For : COMPOSITIONS AND METHODS FOR THE THERAPY AND
DIAGNOSIS OF LUNG CANCER

Docket No. : 210121.475C7

Date : September 20, 2000

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

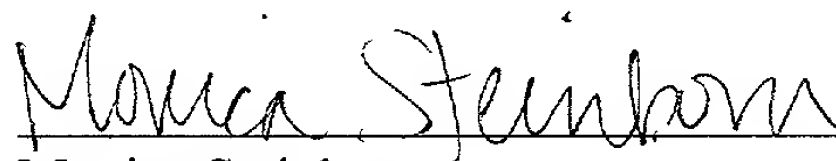
DECLARATION

Sir:

I, Monica Steinborn, in accordance with 37 C.F.R. § 1.821(f) do hereby declare that, to the best of my knowledge, the content of the paper entitled "Sequence Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 20th day of September, 2000.



Monica Steinborn
Biotechnology Paralegal

701 Fifth Avenue, Suite 6300
Seattle, WA 98104-7092
(206) 622-4900
FAX (206) 682-6031

SEQUENCE LISTING

<110> Reed, Steven G.	Henderson, Robert A.
Lodes, Michael J.	Fling, Steven P.
Mohamath, Raodoh	Algate, Paul A.
Secrist, Heather	Indirias, Carol Yoseph
Benson, Darin R.	

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THE THERAPY AND DIAGNOSIS OF LUNG CANCER

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 aagttcagga cacaagcttc tggcccatgc agagcagagg ccatgagggg tcacagcatg 240
 ggtacgggag gaaacactgg gctnaccag atnctggact tgagtcttgc ctctgctgct 300
 tgctgcacag cttctgtcat ggtgctaaac ctgtgacctg cctcacaggc ttagagcatg 360
 cccgtagaag tactctnaac taaratgctt tccacaaatg agatggtttc atgaaaactt 420
 caaatagagg gcctgggcaa aaaaaaaaaa 449

<210> 10
 <211> 538
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(538)
 <223> n = A,T,C or G

<400> 10
 tttttttttt ttcccaaagg cctcaraaca ctagtcttct aattccaagc agaaagttac 60
 atccgccggg atacatgcca cttgggttga taaatcaaaa tacagcatcc ttcagatccc 120

```

tttgctgagc aatacaatta tttgtatatg ttactttttt ttctgttttg ctnaaagatt 180
tgatatgagc tgaggaaaat gaagcentta ctgctatnag atctnatccc tttccaccac 240
ctttcaggga tnttggcact gcayatattc agaattcccc nnagtcgctn gtgataaaaa 300
tgtcttcaga gatggcagaa tatgtttcct ttggtacatg ttcattaaaa atatacacgt 360
gctcactact gtggatatgt atgtnttgac cgatnacaca ggctgattta gggaagagat 420
aaaagcacac ttngaattta ttagcctttc accnagacta anattctgaa attaagaatg 480
tattccttgg tcaacaattt tcctcttttc ttagccctct tacattgtan tggactga 538

```

```

<210> 11
<211> 543
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(543)
<223> n = A,T,C or G

```

```

<400> 11
tttttttttt ttgccacag ctgccatctt tgtgtgataa ggccaacctt ctatgggaat 60
caaccctcgc catcccagca aatcccctct ctcccttctc atgggagtg cttgtattca 120
tcaggcatct gggacttgat gtgggtntgg gatttgaaat cagagcacct nggtctctst 180
caccattctn tcacttatta gctctnacct tgggtnaata cctgccttag tgtcntaggt 240
acaatatgaa tattgtctat ttctcaggga ttgcaatgac nagtnnatna gtgcatgaga 300
gggtaaaacc acaggggtact ccgctcctcc naagaatgga gaattttttc tagaagccca 360
natntgcttg gaagggttggc caccnagagc cnnaatcttc ttttatttnc cactgaangc 420
ctaagaggna attctgaact catccccna tgacctctcc cgaatmagaa tatctctggc 480
acttaccata ttttcttgcc ctcttccact tacnaaactc ctttattcct taacnggacg 540
aaa 543

```

```

<210> 12
<211> 329
<212> DNA
<213> Homo sapien

```

```

<400> 12
cgatgacttg ggcagtgagt gggcctcctg ccaggtggca gggcacagct tagaccaaac 60
ccttggcctc cccctctctg agstacctct gaccaagaag gaaactagca agcctatgct 120
ggcaagacca taggtggggg gctgggaatc ctgggggccc gctggcaccc actcctggtg 180
ctcaagggag agaccactt gttcagatgc atrggcctca ggcggttcaa ggcrgtctta 240
gagccacaga gtcaaataaa aatcaatttt gagagaccac agcacctgct gctttgatcg 300
tgatgttcaa ggcaagttgc aagtcacgc 329

```

```

<210> 13
<211> 314
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(314)
<223> n = A,T,C or G

```

```

<400> 13

```



```

cgatgacttg caccgaggag ctgtgacagt ggcttggaag cagatggcag ccccgtaag      60
gcgggagtg agaccaccaa accctccaaa cagagcaaca actagtacgc ggccagcagc      120
tacctgagcc tgacgcccga gcagtgggaag tcccacagaa gctacagctg ccaggtcacg      180
catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttcata ggttcccnac      240
tctnacccca cccacgggag cctgganctg cangatcccg ggggaagggt ctctctcccc      300
atcccaagtc atcg                                     314

```

```

<210> 14
<211> 691
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(691)
<223> n = A,T,C or G

```

```

<400> 14
cgattacttg cacaatgcan attagaaccc aaatgaaggg tacaaccag atcttctggc      60
ttccagttca gtgctgctgg gtttttctta ctaaaccaaa acaatkaaga gcatagaagg      120
gaagagaaga ataaagtcta ttttggtctt tggtagcchg ggtaangaga atgctstcac      180
tctacnagaa aaccnnaagt gaaccgggt aatcaggacc gtgcttgga agggagcagg      240
ggcattacct ttcaacacca gaggttcttt gccttctctc tgcagggact cgargactat      300
gtgaagtggc tgggarggca tcaactgggt tggttcattg gtrttctcat cataaactat      360
natttctttg gaaaaagatc ctcttgaaag artccttgcc ttccctacag gaaatcaagt      420
ctaggacagt gatcttgccc ctgcttgcas tctccgcccg ctgatcttat csgscccagt      480
tkatgtgsam cgctccttgg atrtkactct tgttttwctc cvaggaagg gcytgcmagt      540
ccnwtnaatg amssgggccc ttaactccgg scrpgtnamy ncttgscctsc rattttgggt      600
ycytcttcyt ttgscmagg tcktcnaaac cacttngttr aattccccgg scgcctkgc      660
nggtycaacc wttttgggaa mamcycccc c                                     691

```

```

<210> 15
<211> 355
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A,T,C or G

```

```

<400> 15
acctgaactg tgtgttgaag agtgatgtcc tgctgcctgg agctcaagtc actactgatg      60
accgtgccta tgtccgacag ctagttncct ccattggatgt gactgagacc aatgtcttct      120
tcyaccctcg gctcttacct ttgacnaagt ctcccgttga gagtactacc gaaccaccag      180
cagttcgagc ctctnaagag cgtctaagcg atggggatat atatctactg gagaatgggc      240
tcaacctctt cctctgggtg ggagcaagcg tccagcaggg tgttggtccag agccttttca      300
gcgtctcttc cttcagtcag atcaccagtg gtntgagtgt tctgccagtt caggt          355

```

```

<210> 16
<211> 522
<212> DNA
<213> Homo sapien

```

<220>
 <221> misc_feature
 <222> (1)...(522)
 <223> n = A,T,C or G

<400> 16
 tcagtccagt gaggtggaag acttcgaggc tcgtgggagc cgcttctcca agtctgctga 60
 tgagagacag cgcattgctgg tgcagcgtan ggacgaactc ctccagcaag ctccgagacg 120
 tttcttgaac aaaagtctctg aagatgatgc ggcctcagag agcttctctc cctcggaagg 180
 tgcgtcctct gaccccgctga cctnccgtcg aangatgctg gctgccgccg cggaacggan 240
 gcttcagaag cagcagacct cctnccgtc ccttgccttc ctccagctgcc tcctgcgccc 300
 tgtgcccggc tgactggagg aggctgtcc aattctgccc gcccctatgga aaagcgggct 360
 tgactgcatt gccgctgtat naaagcatgt ggtcttacag tgttnggaen gctnatnaat 420
 ttnatcctnc tntgtaatac ttcctatgtg acatttctct tccccttgga aacactgcan 480
 attttaactg tgagtttggat ctcttctnct gttactggac tg 522

<210> 17
 <211> 317
 <212> DNA
 <213> Homo sapien

<400> 17
 gtgtcgcgaa ttcgcggtgg tgctaagaaa aggaagaaga agtcttacac cactcccaag 60
 aaggataagc accagagaaa gaagggttcag ccggccgtcc tgaaatatta taagggtggat 120
 gagaatggca aaattagttg ccttcgtcga gattgcccct ctgatgaatg tgggtgctggg 180
 gtgtttatgg caagtcactt tgacagacat tattgtggca aatgttgtct gaccactgt 240
 ttcaactaac cagaagacaa gtaactgtat gagttaatta aagacatgaa ctaaaaaaaaa 300
 aaaaaaaaaa actcgag 317

<210> 18
 <211> 392
 <212> DNA
 <213> Homo sapien

<400> 18
 tggagatttc taatgaggtg aggaagttcc gtacattgac agaattgatc ctccatgctc 60
 aggaacatgt taaaaatcct taaaaaggca aaaaactcaa gaaacacca gacttcccca 120
 agaagcccct gacccttat ttcgcttct tcatggagaa gcgggccaag tatgcgaaac 180
 tccaccctca gatgagcaac ctggacctga ccaagattct gtccaagaaa tacaaggagc 240
 ttccggagaa gaagaagatg aaatatgttc cggacttcca gagaagagaa acaggagtgc 300
 gaggcgaacc tggcccgtatt caggaggat cccccccacc ttatccagaa tgccaagaat 360
 cggacatccc agagaagccc caagaccccc cg 392

<210> 19
 <211> 2624
 <212> DNA
 <213> Homo sapien

<400> 19
 gaaacagtga gaaggagatt cctgtgctca atgagctgcc agtccccatg gtggcccgt 60
 acattcgcat aaaccctcag tcttggtttg ataacgggag catctgcatg aggatggaga 120
 tcttgggctg cccactgccg gatcctaata actattatca ccgacgtaat gagatgacca 180
 ccacggatga cctggatttt aagcaccaca actattagga aatgcgccag ttgatgaagg 240
 ttgtcaatga aatgtgcccc aatattacca ggatttacaa cattggcaaa agccaccagg 300

gcctgaaatt	gtatgcggtg	gagatctctg	accatcctgg	ggaacatgaa	gttggtgagc	360
ccgagttcca	ctacatcgca	ggggcccacg	gcaatgaggt	tctgggacga	gaactgctgc	420
tgctgctgct	gcacttcctc	tgccaggaat	actcggcgca	gaacgcacgc	atcgtccgct	480
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tcgatatcaa	caacaacttt	ccggatttaa	actcgtctgt	ctgggaggca	gaggaccagc	660
agaatgcccc	aaggaaggtc	cccaaccact	acattgccat	ccctgagtgg	tttctgtctg	720
agaatgccac	agtggccaca	gagaccagag	ccgtcatcgc	ctggatggag	aagatcccgt	780
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tgcggtccct	gtggaagacc	caggagcaca	ccccaacacc	tgatgatcat	gtgttccgct	900
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atttacaagg	gaaagggatt	tcaaatgctg	tcctctctgt	ggaagggtgt	aaccatgaca	1260
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gagctactcg	gtgtgacttc	accctcacia	agaccaacct	ggctaggata	agagaaatta	1440
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aataaaaatc	cactccagta	gtaactctgt	agcaggcttt	ccctgttgtt	ttgactgtaa	1620
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gtctgagatt	ctaaaaaggg	tgcttgacca	ctggccagga	agggaaatca	ggccttcccc	1860
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acccagggaa	tcctttgccc	cagatgttat	catttgagat	gctcttatgc	agcctaagaa	1980
aatccatcct	ctctggcccc	aggggacaag	ccaagctgct	atgtacacac	tcggtgttct	2040
attgacaata	gaggcattta	ttaccaagtg	tgcctcgtcg	agtcctaaat	cagctctgtt	2100
cctttttcca	acaaagcttg	tcttcctaag	agcagacaga	agtggagagc	acccaagaat	2160
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ggacacgtca	gtctgggaga	ggtggttgaa	tcattgtgta	agggaatagt	gtatctaata	2520
tgtgttgatc	ctgctgcctt	gttgacctgg	agagaatgaa	acaaacaaac	acataaacia	2580
ataaagcaaa	tggttaagatt	aaaaaaaaaa	aaaaaaaaact	cgag		2624

<210> 20

<211> 488

<212> DNA

<213> Homo sapien

<400> 20

ctttcaaccc	gcgctcgccg	gctccagccc	cgcgcgcccc	caccccttgc	cctcccggcg	60
gctccgcagg	gtgaggtggc	tttgaccccc	ggttgccccg	ccagcacgac	cgaggaggtg	120
gctggacagc	tggaggatga	acggagaagc	cgactgcccc	acagacctgg	aatggccgc	180
ccccagaggg	caagaccgtt	ggtcccagga	agacatgctg	actttgctgg	aatgcatgaa	240
gaacaacctt	ccatccaatg	acagctccca	gttcaaaacc	acccaaacac	acatggaccg	300
ggaaaaagtt	gcattgaaag	acttttcttg	agacatgtgc	aagctcaaat	gggtcgagat	360
ctctaataag	gtgaggaagt	tccgtacatt	gacagaattg	atcctcgata	ctcaggaaca	420
tgtttaaaat	ccttacaag	gcaaaaaatc	aagaaacacc	ccgacttccc	cgagaaagcc	480

cctaaccc

488

<210> 21
 <211> 391
 <212> DNA
 <213> Homo sapien

<400> 21

atggaattgt	ggttttctct	ttgggatcaa	tgggtctcaga	aattccagag	aagaaagctg	60
tggcgattgc	tgatgctttg	ggcaaaatcc	ctcagacagt	cctgtggcgg	tacactggaa	120
cccgaccatc	gaatcttgcg	aacaacacga	tacttgttca	gtggctaccc	caaaacgatc	180
tgcttggtca	cccaatgacc	cgtgccttta	tcacccatgc	tagttcccat	ggtgttaatg	240
aaagcatatg	caatggcggt	cccatgggtga	tgataaccctt	atttggtgat	cagatggaca	300
atgcaaagcg	cagggagact	aagggagctg	gagtgaccct	gaatgttctg	gagatgactt	360
ctgaagatct	agaagatgct	ctgaagagca	g			391

<210> 22
 <211> 1320
 <212> DNA
 <213> Homo sapien

<400> 22

aatctgctgg	gaatttcttg	ggttgacagc	tcttggtatcc	ctattttgaa	cagtggtagt	60
gtcctggatt	acttttcaga	aagaagtaat	cctttttatg	acagaacatg	taataatgaa	120
gtggtcaaaa	tgcagaggct	aacattagaa	cacttgaatc	agatggttgg	aatcgagtac	180
atccttttgc	atgctcaaga	gccatttctt	ttcatcattc	ggaagcaaca	gcggcagtc	240
cctgccaag	ttatcccact	agctgattac	tatatcattg	ctggagtgat	ctatcaggca	300
ccagacttgg	gatcagttat	aaactctaga	gtgcttactg	cagtgcattg	tattcagtca	360
gcttttgatg	aagctatgtc	atactgtcga	tatcatcctt	ccaaagggtg	ttggtggcac	420
ttcaaagatc	atgaagagca	agataaagtc	agacctaaag	ccaaaaggaa	agaagaacca	480
agctctat	ttcagagaca	acgtgtggat	gctttacttt	tagacctcag	acaaaaat	540
ccacccaaat	ttgtgcagct	aaagcctgga	gaaaagcctg	ttccagtggg	tcaaacaaag	600
aaagaggcag	aacctatacc	agaaactgta	aaacctgagg	agaaggagac	cacaaagaat	660
gtacaacaga	cagtgagtgc	taaaggcccc	cctgaaaaac	ggatgagact	tcagtgagta	720
ctggacaaaa	gagaagcctg	gaagactcct	catgctagtt	atcatacctc	agtactgtgg	780
ctcttgagct	ttgaagtact	ttattgtaac	cttcttattt	gtatggaatg	cgcttatttt	840
ttgaaaggat	attaggccgg	atgtgggtggc	tcacgcctgt	aatcccagca	ctttgggagg	900
ccatggcggg	tggatcactt	gaggtcagaa	gttcaagacc	agcctgacca	atatggtgaa	960
accccgcttc	tactaaaaat	acaaaaatta	gccgggcgtg	gtggcgggcg	cccatagtc	1020
cagctactcg	ggaggctgag	acaggagact	tgcttgaacc	cgggaggtgg	aggttgccct	1080
gagctgatca	tcctgctgtt	gcactccagc	ttgggcgaaa	gagcgagact	ttgtctctat	1140
aaagaaggaa	agatattatt	cccatcatga	tttcttgatg	atatgtgtaa	tatgtttttt	1200
gtaacctttc	ctttcccggg	cttgagcaac	ctacacactc	acatgtttta	tggtagatat	1260
gttttaaagc	aagataaagg	tattgggtttt	aaaaaaaaaa	aaaaaaaaaa	aaaactcgag	1320

<210> 23
 <211> 633
 <212> DNA
 <213> Homo sapien

<400> 23

ctaagggcag	tgaagggtgaa	aaccctctca	cgggtcccagg	gagggagaa	gaaggcatgc	60
tgatgggggt	taagccgggg	gaggacgcat	cggggcctgc	tgaagacctt	gtgagaagat	120
ctgagaaaga	tactgcagct	gttgtctcca	gacagggcag	ctccctgaac	ctctttgaag	180

atgtgcagat	cacagaacca	gaagctgagc	cagagtccaa	gtctgaaccg	agacctccaa	240
tttcctctcc	gagggctccc	cagaccagag	ctgtcaagcc	ccgacttcat	cctgtgaagc	300
caatgaatgc	cacggccacc	aagggttgcta	actgcagctt	gggaactgcc	accatcatcg	360
gtgagaactt	gaacaatgag	gtcatgatga	agaaatacag	cccctcggac	cctgcatttg	420
catatgcgca	gctgaccac	gatgagctga	ttcagctggt	cctcaaacag	aaggaaacga	480
taagcaagaa	ggagttccag	gtccgcgagc	tggaagacta	cattgacaac	ctgctcgtca	540
gggtcatgga	agaaaccccc	aatatcctcc	gcaccccgac	tcagggttggc	aaaaaagcag	600
gaaagatgta	aattagcaga	aaaaaaactc	gag			633

<210> 24

<211> 1328

<212> DNA

<213> Homo sapien

<400> 24

gtaaacgctc	tcggaattat	ggcggcggtg	gatatccgag	acaatctgct	gggaattttct	60
tgggttgaca	gctcttgat	ccctattttg	aacagtggta	gtgtcctgga	ttacttttca	120
gaaagaagta	atccttttta	tgacagaaca	tgtaataatg	aagtgggtcaa	aatgcagagg	180
ctaacattag	aacacttgaa	tcagatgggt	ggaatcgagt	acatcctttt	gcatgctcaa	240
gagcccattc	ttttcatcat	tcggaagcaa	cagcggcagt	cccctgccca	agttatccca	300
ctagctgatt	actatatcat	tgctggagtg	atctatcagg	caccagactt	gggatcagtt	360
ataaactcta	gagtgttac	tgcatgtcat	ggtattcagt	cagcttttga	tgaagctatg	420
tcatactgtc	gatatcatcc	ttccaaaggg	tattggtggc	acttcaaaga	tcatgaagag	480
caagataaag	tcagaccta	agccaaaagg	aaagaagaac	caagctctat	ttttcagaga	540
caacgtgtgg	atgctttact	tttagacctc	agacaaaaaa	tttccaccca	aatttgtgca	600
gtggatcaaa	caaagaaaga	ggcagaacct	ataccagaaa	ctgtaaaacc	tgaggagaag	660
gagaccacaa	agaatgtaca	acagacagt	agtgtctaa	gccccctga	aaaacggatg	720
agacttcagt	gagtactgga	caaaagagaa	gcctggaaga	ctcctcatgc	tagttatcat	780
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tgaccaatat	ggtgaaaccc	cgtctctact	aaaaatacaa	aaattagccg	ggcgtggtgg	1020
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aggtggaggt	tgccctgagc	tgattatcat	gctgttgac	tccagcttgg	gcgacagagc	1140
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ttgtgatatg	tcttctgtaa	cctttcctct	cccggacttg	agcaacctac	acactcacat	1260
gtttactggt	agatatgttt	aaaagcaaaa	taaaggattt	tgtataaaaa	aaaaaaaaaa	1320
aaactcga						1328

<210> 25

<211> 1758

<212> DNA

<213> Homo sapien

<400> 25

gttttttttt	tttttttttt	aaagagttgc	aacaattcat	ctttattttct	tatttttctc	60
tggagatgca	gaatttggtg	tattttcacc	caagtatatt	tgggatagtt	ggctcctcgc	120
tgggtcagga	tggttggtg	ccttctcccc	tggtcatggt	ctcttctctg	cagggcgagg	180
ggcagggagc	tagtaaaacc	tcgcaatgac	agccgcaatg	gcagacccaa	tggagcccag	240
gatgaacttg	gtcaatccgg	agagtccagt	tgctcccagt	gactgcagag	tagccacaag	300
gctgcccag	gcaactccac	ccccattggc	aatggccgcc	gcggacatca	tcttggctgc	360
tatggaggac	gagggcattc	ccgccgcagt	gaagcccatg	gcactgagtg	gcggcggtgg	420
atatccgaga	caatctgctg	ggaatttctt	gggttgacag	ctcttggtac	cctattttga	480
acagtggtag	tgctctggat	tacttttcag	aaagaagtaa	tcctttttat	gacagaacat	540

gtaataatga	agtgggtcaaa	atgcagagggc	taacattaga	acacttgaat	cagatgggttg	600
gaatcgagta	catccttttg	catgctcaag	agccatttct	tttcatcatt	cggaagcaac	660
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gtattcagtc	agctttttgat	gaagctatgt	catactgtcg	atatcatcct	tccaaaggggt	840
attggtggca	cttcaaagat	catgaagagc	aagataaagt	cagacctaata	gccaaaagga	900
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tttgtctcaa	aaaagaagaa	aagatattat	tcccatcatg	atttcttgtg	aatatttggt	1620
atatgtcttc	tgttaccttt	cctctcccgg	aattgagcaa	cctacacact	cacatgttta	1680
ctggtagata	tgtttaaaag	caaataaagg	tattggtata	tattgcttca	aaaaaaaaaa	1740
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<210> 26

<211> 493

<212> DNA

<213> Homo sapien

<400> 26

gaggcgagcg	gcagggcctg	gtggcgagag	cgcggtgtgc	actgcgcccg	agcatcccag	60
agctttccga	gcggacgagc	cggccgtgcc	gggcatcccc	agcctcgcta	ccctcgagc	120
acacgtcgag	ccccgcacag	gcaaggggtcc	ggaacttagc	ccaaagcacg	tttcccctgg	180
cagcgcagga	gacgcccggc	cgcgcgcccg	cgcaagcccc	cctctcctcc	tttgttccgg	240
gggtcgggcg	ccgctctcct	gccagcgctg	ggatctcggc	cccgggaggc	gggcccgtcg	300
gcgcagccgc	gaagattccg	ttggaactga	cgcagagccg	agtgcagaag	atctgggtgc	360
ccgtggacca	caggccctcg	ttgcccagat	cctgtggggc	aaagctgacc	aactcccccg	420
ccgtcttcgt	catggtgggc	ctcccccgcc	cggggcaaga	cctacttctc	cacgaaagct	480
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<210> 27

<211> 1331

<212> DNA

<213> Homo sapien

<400> 27

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aacatgtaat	aatgaagtgg	tcaaaatgca	gaggctaaca	ttagaacact	tgaatcagat	180
ggttggaatc	gagtacatcc	ttttgcatgc	tcaagagccc	attcttttca	tcattcggaa	240
gcaacagcgg	cagtcccctg	cccaagttat	cccactagct	gattactata	tcattgctgg	300
agtgatctat	caggcaccag	acttggggtc	agttataaac	tctagagtgc	ttactgcagt	360
gcatggtatt	cagtcagctt	ttgatgaagc	tatgtcatac	tgctgatata	atccttccaa	420
aggggtattg	tggcacttca	aagatcatga	agagcaagat	aaagtcagac	ctaaagccaa	480
aaggaaagaa	gaaccaagct	ctatttttca	gagacaacgt	gtggatgctt	tactttttaga	540
cctcagacaa	aaatttccac	ccaaatttgt	gcagctaaag	cctggagaaa	agcctgttcc	600

agtggatcaa	acaaagaaag	aggcagaacc	tataaccagaa	actgtaaaac	ctgaggagaa	660
ggagaccaca	aagaatgtac	aacagacagt	gagtgtctaaa	ggccccctg	aaaaacggat	720
gagacttcag	tgagtactgg	acaaaagaga	agcctggaag	actcctcatg	ctagttatca	780
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ggaatgctgt	tattttttga	aaggatatta	ggccggatgt	ggtggctcac	gcctgtaatc	900
ccagcacttt	gggaggccat	ggcgggtgga	tcacttgagg	tcagaagttc	aagaccagcc	960
tgaccaatat	ggtgaaaccc	cgtctctact	aaaaatacaa	aaattagccg	ggcgtggtgg	1020
cgggcgcccc	tagtcccagc	tactcgggag	gctgagacag	gagacttgct	tgaacccggg	1080
aggtggaggt	tgccctgagc	tgattatcat	gctgttgac	tccagcttgg	gcgacagagc	1140
gagactttgt	ctcaaaaaaa	gaagaaaaga	tattattccc	atcatgattt	cttgtgaata	1200
tttgttatat	gtcttctgta	acctttcctc	tcccggactt	gagcaaccta	cacactcaca	1260
tgtttactgg	tagatatgtt	taaaagcaaa	ataaagggtat	tggtataaaa	aaaaaaaaaa	1320
aaaaactcga	g					1331

<210> 28

<211> 1333

<212> DNA

<213> Homo sapien

<400> 28

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ctatttttgaa	cagtggtagt	gtcctggatt	acttttcaga	aagaagtaat	cctttttatg	120
acagaacatg	taataatgaa	gtggtcaaaa	tgcagaggct	aacattagaa	cacttgaatc	180
agatggttgg	aatcgagtac	atccttttgc	atgctcaaga	gccattctt	ttcatcattc	240
ggaagcaaca	gcggcagtcc	cctgcccagg	ttatcccact	agctgattac	tatatcattg	300
ctggagtgat	ctatcaggca	ccagacttgg	gatcagttat	aaactctaga	gtgcttactg	360
cagtgcattg	tattcagtca	gcttttcatg	aagctatgtc	atactgtcga	tatcatcctt	420
ccaaagggtg	ttggtggcac	ttcaaagatc	atgaagagca	agataaagtc	agacctaaag	480
ccaaaaggaa	agaagaacca	agctctatct	ttcagagaca	acgtgtggat	gctttacttt	540
tagacctcag	acaaaaatct	ccacccaaat	ttgtgcagct	aaagcctgga	gaaaagcctg	600
ttccagtggg	tcaaacaagg	aaagaggcag	aacctatacc	agaaactgta	aaacctgagg	660
agaaggagac	cacaaagaat	gtacaacaga	cagtgagtgc	taaaggcccc	cctgaaaaac	720
ggatgagact	tcagtgtgta	ctggacaaaa	gagaagcctg	gaagactcct	catgctagtt	780
atcatacctc	agtactgtgg	ctcttgagct	ttgaagtact	ttattgtaac	cttcttatct	840
gtatggaatg	cgcttatctt	ttgaaaggat	attaggccgg	atgtgggtgg	tcacgcctgt	900
aatcccagca	ctttgggagg	ccatggcggg	tggatcactt	gaggtcagaa	gttcaagacc	960
agcctgacca	atatggtgaa	accccgctct	tactaaaaat	acaaaaatta	gccgggctg	1020
gtggcggggc	cccatagtcc	cagctactcg	ggaggctgag	acaggagact	tgcttgaacc	1080
cgggaggtgg	aggttgccct	gagctgatta	tcagtctgtt	gcactccagc	ttgggcgaca	1140
gagcgagact	ttgtctcaaa	aaagaagaaa	agatattatt	cccatcatga	tttcttgtga	1200
atatttgtga	tatgtcttct	gtaacctttc	ctctcccggg	cttgagcaac	ctacacactc	1260
acatgtttac	tggtagatat	gtttaaaagc	aaaataaagg	tatttgtata	aaaaaaaaaa	1320
aaaaaaactc	gag					1333

<210> 29

<211> 813

<212> DNA

<213> Homo sapien

<400> 29

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accgagacaa	cagccccagc	tctgtgtgct	gcctcttcat	tgcttcacac	atcgggtttg	120
actggcccgg	ggtctgggtc	cacctggaca	tcgctgctcc	agtgcattgt	ggcgagcgag	180
ccacaggctt	tgggggtggc	ctcctactgg	ctcttttttg	ccgtgcctcc	gaggacccgc	240

tgctgaacct	ggtatccccg	ctggactgtg	aggtggatgc	ccaggaaggc	gacaacatgg	300
ggcgtgactc	caagagacgg	aggctcgtgt	gagggctact	tcccagctgg	tgacacaggg	360
ttccttacct	cattttgcac	tgactgattt	taagcaattg	aaagattaac	taactcttaa	420
gatgagtttg	gcttctcctt	ctgtgcccag	tggtgacagg	agtgagccat	tcttctctta	480
gaagcagctt	aggggcttgg	tggggctctg	agaaaattgt	cacagacccc	ataggtctcc	540
atctgtaagc	tctgtccctt	gtcctccacc	ctggtcttta	gagccacctc	aggtcaccct	600
ctgtagtgag	tgtacttcct	gacccaggcc	cttgctcaag	ctggggctcc	ctgggggtgc	660
taaccagccc	tgggtagatg	tgactggctg	ttagggaccc	cattctgtga	agcaggagac	720
cctcacagct	cccaccaacc	cccagttcac	ttgaagttga	attaaatatg	gccacaacat	780
aaaaaaaaaa	aaaaaaaaaa	aaaaaaactc	gag			813

<210> 30

<211> 1316

<212> DNA

<213> Homo sapien

<400> 30

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cagtccaatc	atagaaaaga	tggaaaaaag	gacatgtgcc	ctgtgccctg	aaggccacga	120
gtggagtcaa	atatactttt	caccatcagg	aaatatagtt	gctcatgaaa	actgtttgct	180
gtattcatca	ggactgggtg	agtgtgagac	tcttgatcta	cgtaatacaa	ttagaaactt	240
tgatgtcaaa	tctgtaaaga	aagagatctg	gagaggaaga	agattgaaat	gctcattctg	300
taacaaagga	ggcgccaccg	tgggggtgtg	tttatggttc	tgtagaaga	gttaccacta	360
tgtctgtgcc	aaaaaggacc	aagcaattct	tcaagttgat	ggaaaccatg	gaacttacia	420
attattttgc	ccagaacatt	ctccagaaca	agaagaggcc	actgaaagtg	ctgatgaccc	480
aagcatgaag	aagaagagag	gaaaaaacia	acgcctctca	tcaggccctc	ctgcacagcc	540
aaaaacgatg	aatgtagta	acgccaaaag	acatatgaca	gaagagcctc	atggtcacac	600
agatgcagct	gtcaaactct	cttttcttaa	gaaatgccag	gaagcaggac	ttcttactga	660
actatttgaa	cacatactag	aaaatatgga	ttcagttcat	ggaagacttg	tggatgagac	720
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gcaaaggcag	atgaagcagc	agcttgaggc	acttgcagac	ttacaacaaa	gcttgtgctc	900
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tgaggaccac	cagtaaaagc	tgttcctcag	gaaaactgga	tggggcctcc	atgttctcca	1020
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gctttgctca	gccttaaagt	gaatcttaga	gctttctctt	gcttctgcta	ctcctacaga	1140
tggcctcatc	atgggtctcca	ctcagtatta	ataactccat	cagcatagag	caaactcaac	1200
actgtgcatt	gcacactgtt	accatgggtt	tatgctcact	atcatatcac	attgccaata	1260
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<210> 31

<211> 1355

<212> DNA

<213> Homo sapien

<400> 31

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ctattttgaa	cagtggtagt	gtcctggatt	acttttcaga	aagaagtaat	cctttttatg	120
acagaacatg	taataatgaa	gtgggtcaaaa	tgcagaggct	aacattagaa	cacttgaatc	180
agatggtttg	aatcgagtac	atccttttgc	atgctcaaga	gcccattctt	ttcatcattc	240
ggaagcaaca	gcggcagtcc	cctgcccagg	ttatccact	agctgattac	tatatcattg	300
ctggagtgat	ctatcaggca	ccagacttgg	gatcagttat	aaactctaga	gtgcttactg	360
cagtgcattg	tattcagtca	gcttttgatg	aagctatgtc	atactgtcga	tatcatcctt	420
ccaaagggtg	ttgggtggcac	ttcaaagatc	atgaagagca	agataaagtc	agacctaaag	480

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ccaaaaggaa agaagaacca agctctatatt ttcagagaca acgtgtggat gctttacttt 540
tagacctcag acaaaaattt ccacccaaat ttgtgcagct aaagcctgga gaaaagcctg 600
ttccagtgga tcaaacaaag aaagaggcag aacctatacc agaaactgta aaacctgagg 660
agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 720
ggatgagact tcagttagta ctggacaaaa gagaagcctg gaagactcct catgctagtt 780
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cgggaggtgg aggttgccct gagctgatta tcatgctgtt gcactccagc ttgggcgaca 1140
gaacgagact ttgtctcaaa aaaagaagaa aagatattat tcccatcatg atttcttggtg 1200
aatatttggt atatgtcttc tggtaacctt tcctctcccg gacttgaagc aacctcacac 1260
actcacatgt ttactggtag atatgtttta aaagcaaaat aaaggtattt gtttttccaa 1320
aaaaaaaaa aaaaaaaaaa aaaaaaaaac tcgag 1355

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<210> 32
<211> 80
<212> PRT
<213> Homo sapien

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<400> 32
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Val Ser Arg Ile Arg Gly Gly Ala Lys Lys Arg Lys Lys Lys Ser Tyr
 1           5           10           15
Thr Thr Pro Lys Lys Asp Lys His Gln Arg Lys Lys Val Gln Pro Ala
          20          25          30
Val Leu Lys Tyr Tyr Lys Val Asp Glu Asn Gly Lys Ile Ser Cys Leu
          35          40          45
Arg Arg Glu Cys Pro Ser Asp Glu Cys Gly Ala Gly Val Phe Met Ala
          50          55          60
Ser His Phe Asp Arg His Tyr Cys Gly Lys Cys Cys Leu Thr His Cys
65           70           75           80

```

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<210> 33
<211> 130
<212> PRT
<213> Homo sapien

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<400> 33
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Glu Ile Ser Asn Glu Val Arg Lys Phe Arg Thr Leu Thr Glu Leu Ile
 1           5           10           15
Leu Asp Ala Gln Glu His Val Lys Asn Pro Tyr Lys Gly Lys Lys Leu
          20          25          30
Lys Lys His Pro Asp Phe Pro Lys Lys Pro Leu Thr Pro Tyr Phe Arg
          35          40          45
Phe Phe Met Glu Lys Arg Ala Lys Tyr Ala Lys Leu His Pro Gln Met
          50          55          60
Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
65           70           75           80
Pro Glu Lys Lys Lys Met Lys Tyr Val Pro Asp Phe Gln Arg Arg Glu
          85          90          95
Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
          100         105         110
Pro Tyr Pro Glu Cys Gln Glu Ser Asp Ile Pro Glu Lys Pro Gln Asp

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115 120 125
 Pro Pro
 130

 <210> 34
 <211> 506
 <212> PRT
 <213> Homo sapien

 <400> 34
 Asn Ser Glu Lys Glu Ile Pro Val Leu Asn Glu Leu Pro Val Pro Met
 1 5 10 15
 Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
 20 25 30
 Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro
 35 40 45
 Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Thr Asp Asp Leu
 50 55 60
 Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
 65 70 75 80
 Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
 85 90 95
 Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
 100 105 110
 Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
 115 120 125
 His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu Leu His
 130 135 140
 Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
 145 150 155 160
 Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
 165 170 175
 Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
 180 185 190
 Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
 195 200 205
 Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
 210 215 220
 Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
 225 230 235 240
 Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
 245 250 255
 Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
 260 265 270
 Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
 275 280 285
 His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
 290 295 300
 Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Arg Val Cys
 305 310 315 320
 His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
 325 330 335
 Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
 340 345 350

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<210> 35
<211> 96
<212> PRT
<213> Homo sapien
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<210> 36
<211> 129
<212> PRT
<213> Homo sapien
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<400> 36															
Gly	Ile	Val	Val	Phe	Ser	Leu	Gly	Ser	Met	Val	Ser	Glu	Ile	Pro	Glu
1				5					10					15	
Lys	Lys	Ala	Val	Ala	Ile	Ala	Asp	Ala	Leu	Gly	Lys	Ile	Pro	Gln	Thr
			20					25					30		
Val	Leu	Trp	Arg	Tyr	Thr	Gly	Thr	Arg	Pro	Ser	Asn	Leu	Ala	Asn	Asn
		35					40					45			
Thr	Ile	Leu	Val	Gln	Trp	Leu	Pro	Gln	Asn	Asp	Leu	Leu	Gly	His	Pro
	50					55					60				

Met Thr Arg Ala Phe Ile Thr His Ala Ser Ser His Gly Val Asn Glu
 65 70 75 80
 Ser Ile Cys Asn Gly Val Pro Met Val Met Ile Pro Leu Phe Gly Asp
 85 90 95
 Gln Met Asp Asn Ala Lys Arg Arg Glu Thr Lys Gly Ala Gly Val Thr
 100 105 110
 Leu Asn Val Leu Glu Met Thr Ser Glu Asp Leu Glu Asp Ala Leu Lys
 115 120 125
 Ser

<210> 37
 <211> 238
 <212> PRT
 <213> Homo sapien

<400> 37

Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu
 1 5 10 15
 Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe
 20 25 30
 Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr
 35 40 45
 Leu Glu His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His
 50 55 60
 Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser
 65 70 75 80
 Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val
 85 90 95
 Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu
 100 105 110
 Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr
 115 120 125
 Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His
 130 135 140
 Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro
 145 150 155 160
 Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu
 165 170 175
 Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu Lys Pro Gly Glu Lys
 180 185 190
 Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala Glu Pro Ile Pro Glu
 195 200 205
 Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys Asn Val Gln Gln Thr
 210 215 220
 Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met Arg Leu Gln
 225 230 235

<210> 38
 <211> 202
 <212> PRT
 <213> Homo sapien

<400> 38

Lys Gly Ser Glu Gly Glu Asn Pro Leu Thr Val Pro Gly Arg Glu Lys
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 Glu Gly Met Leu Met Gly Val Lys Pro Gly Glu Asp Ala Ser Gly Pro
 20 25 30
 Ala Glu Asp Leu Val Arg Arg Ser Glu Lys Asp Thr Ala Ala Val Val
 35 40 45
 Ser Arg Gln Gly Ser Ser Leu Asn Leu Phe Glu Asp Val Gln Ile Thr
 50 55 60
 Glu Pro Glu Ala Glu Pro Glu Ser Lys Ser Glu Pro Arg Pro Pro Ile
 65 70 75 80
 Ser Ser Pro Arg Ala Pro Gln Thr Arg Ala Val Lys Pro Arg Leu His
 85 90 95
 Pro Val Lys Pro Met Asn Ala Thr Ala Thr Lys Val Ala Asn Cys Ser
 100 105 110
 Leu Gly Thr Ala Thr Ile Ile Gly Glu Asn Leu Asn Asn Glu Val Met
 115 120 125
 Met Lys Lys Tyr Ser Pro Ser Asp Pro Ala Phe Ala Tyr Ala Gln Leu
 130 135 140
 Thr His Asp Glu Leu Ile Gln Leu Val Leu Lys Gln Lys Glu Thr Ile
 145 150 155 160
 Ser Lys Lys Glu Phe Gln Val Arg Glu Leu Glu Asp Tyr Ile Asp Asn
 165 170 175
 Leu Leu Val Arg Val Met Glu Glu Thr Pro Asn Ile Leu Arg Ile Pro
 180 185 190
 Thr Gln Val Gly Lys Lys Ala Gly Lys Met
 195 200

<210> 39
 <211> 243
 <212> PRT
 <213> Homo sapien

<400> 39

Val Asn Ala Leu Gly Ile Met Ala Ala Val Asp Ile Arg Asp Asn Leu
 1 5 10 15
 Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu Asn Ser
 20 25 30
 Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe Tyr Asp
 35 40 45
 Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr Leu Glu
 50 55 60
 His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His Ala Gln
 65 70 75 80
 Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser Pro Ala
 85 90 95
 Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val Ile Tyr
 100 105 110
 Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu Thr Ala
 115 120 125
 Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr Cys Arg
 130 135 140
 Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His Glu Glu
 145 150 155 160
 Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro Ser Ser

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<210> 40
<211> 245
<212> PRT
<213> Homo sapien
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<210>	41
<211>	163
<212>	PRT

<213> Homo sapien

<400> 41

Gly	Glu	Arg	Gln	Gly	Leu	Val	Ala	Arg	Ala	Arg	Leu	Ser	Leu	Arg	Pro
1				5					10					15	
Ser	Ile	Pro	Glu	Leu	Ser	Glu	Arg	Thr	Ser	Arg	Pro	Cys	Arg	Ala	Ser
			20					25					30		
Pro	Ala	Ser	Leu	Pro	Ser	Gln	His	Thr	Ser	Ser	Pro	Ala	Gln	Ala	Arg
		35					40					45			
Val	Arg	Asn	Leu	Ala	Gln	Ser	Thr	Phe	Pro	Leu	Ala	Ala	Gln	Glu	Thr
	50					55					60				
Pro	Gly	Arg	Ala	Pro	Ala	His	Ala	Pro	Leu	Ser	Ser	Phe	Val	Pro	Gly
65					70					75					80
Val	Gly	Gly	Arg	Ser	Pro	Ala	Ser	Val	Gly	Ile	Ser	Ala	Pro	Gly	Gly
			85						90					95	
Gly	Pro	Ser	Gly	Ala	Ala	Ala	Lys	Ile	Pro	Leu	Glu	Leu	Thr	Gln	Ser
			100					105						110	
Arg	Val	Gln	Lys	Ile	Trp	Val	Pro	Val	Asp	His	Arg	Pro	Ser	Leu	Pro
		115					120					125			
Arg	Ser	Cys	Gly	Pro	Lys	Leu	Thr	Asn	Ser	Pro	Ala	Val	Phe	Val	Met
	130					135					140				
Val	Gly	Leu	Pro	Arg	Pro	Gly	Gln	Asp	Leu	Leu	Leu	His	Glu	Ser	Leu
145					150					155					160
Leu	Ala	Ala													

<210> 42

<211> 243

<212> PRT

<213> Homo sapien

<400> 42

Val	Asp	Ile	Arg	Asp	Asn	Leu	Leu	Gly	Ile	Ser	Trp	Val	Asp	Ser	Ser
1				5					10					15	
Trp	Ile	Pro	Ile	Leu	Asn	Ser	Gly	Ser	Val	Leu	Asp	Tyr	Phe	Ser	Glu
			20					25					30		
Arg	Ser	Asn	Pro	Phe	Tyr	Asp	Arg	Thr	Cys	Asn	Asn	Glu	Val	Val	Lys
		35					40					45			
Met	Gln	Arg	Leu	Thr	Leu	Glu	His	Leu	Asn	Gln	Met	Val	Gly	Ile	Glu
	50					55					60				
Tyr	Ile	Leu	Leu	His	Ala	Gln	Glu	Pro	Ile	Leu	Phe	Ile	Ile	Arg	Lys
65					70					75					80
Gln	Gln	Arg	Gln	Ser	Pro	Ala	Gln	Val	Ile	Pro	Leu	Ala	Asp	Tyr	Tyr
			85						90					95	
Ile	Ile	Ala	Gly	Val	Ile	Tyr	Gln	Ala	Pro	Asp	Leu	Gly	Ser	Val	Ile
			100					105						110	
Asn	Ser	Arg	Val	Leu	Thr	Ala	Val	His	Gly	Ile	Gln	Ser	Ala	Phe	Asp
		115					120						125		
Glu	Ala	Met	Ser	Tyr	Cys	Arg	Tyr	His	Pro	Ser	Lys	Gly	Tyr	Trp	Trp
	130					135					140				
His	Phe	Lys	Asp	His	Glu	Glu	Gln	Asp	Lys	Val	Arg	Pro	Lys	Ala	Lys
145					150					155					160
Arg	Lys	Glu	Glu	Pro	Ser	Ser	Ile	Phe	Gln	Arg	Gln	Arg	Val	Asp	Ala
				165					170					175	

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<210> 43
<211> 244
<212> PRT
<213> Homo sapien
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<210> 44
<211> 109
<212> PRT
<213> Homo sapien
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<400> 44

Glu	Leu	His	Phe	Ser	Glu	Phe	Thr	Ser	Ala	Val	Ala	Asp	Met	Lys	Asn
1				5					10					15	
Ser	Val	Ala	Asp	Arg	Asp	Asn	Ser	Pro	Ser	Ser	Cys	Ala	Gly	Leu	Phe
			20					25					30		
Ile	Ala	Ser	His	Ile	Gly	Phe	Asp	Trp	Pro	Gly	Val	Trp	Val	His	Leu
		35					40					45			
Asp	Ile	Ala	Ala	Pro	Val	His	Ala	Gly	Glu	Arg	Ala	Thr	Gly	Phe	Gly
	50					55					60				
Val	Ala	Leu	Leu	Leu	Ala	Leu	Phe	Gly	Arg	Ala	Ser	Glu	Asp	Pro	Leu
65					70					75					80
Leu	Asn	Leu	Val	Ser	Pro	Leu	Asp	Cys	Glu	Val	Asp	Ala	Gln	Glu	Gly
				85					90					95	
Asp	Asn	Met	Gly	Arg	Asp	Ser	Lys	Arg	Arg	Arg	Leu	Val			
			100					105							

<210> 45

<211> 324

<212> PRT

<213> Homo sapien

<400> 45

Arg	Arg	Pro	Val	Met	Ala	Gln	Glu	Thr	Ala	Pro	Pro	Cys	Gly	Pro	Val
1				5					10					15	
Ser	Arg	Gly	Asp	Ser	Pro	Ile	Ile	Glu	Lys	Met	Glu	Lys	Arg	Thr	Cys
			20					25					30		
Ala	Leu	Cys	Pro	Glu	Gly	His	Glu	Trp	Ser	Gln	Ile	Tyr	Phe	Ser	Pro
		35					40					45			
Ser	Gly	Asn	Ile	Val	Ala	His	Glu	Asn	Cys	Leu	Leu	Tyr	Ser	Ser	Gly
	50					55					60				
Leu	Val	Glu	Cys	Glu	Thr	Leu	Asp	Leu	Arg	Asn	Thr	Ile	Arg	Asn	Phe
65					70					75					80
Asp	Val	Lys	Ser	Val	Lys	Lys	Glu	Ile	Trp	Arg	Gly	Arg	Arg	Leu	Lys
				85					90					95	
Cys	Ser	Phe	Cys	Asn	Lys	Gly	Gly	Ala	Thr	Val	Gly	Cys	Asp	Leu	Trp
			100					105					110		
Phe	Cys	Lys	Lys	Ser	Tyr	His	Tyr	Val	Cys	Ala	Lys	Lys	Asp	Gln	Ala
		115					120					125			
Ile	Leu	Gln	Val	Asp	Gly	Asn	His	Gly	Thr	Tyr	Lys	Leu	Phe	Cys	Pro
	130					135					140				
Glu	His	Ser	Pro	Glu	Gln	Glu	Glu	Ala	Thr	Glu	Ser	Ala	Asp	Asp	Pro
145					150					155					160
Ser	Met	Lys	Lys	Lys	Arg	Gly	Lys	Asn	Lys	Arg	Leu	Ser	Ser	Gly	Pro
				165					170					175	
Pro	Ala	Gln	Pro	Lys	Thr	Met	Lys	Cys	Ser	Asn	Ala	Lys	Arg	His	Met
			180					185					190		
Thr	Glu	Glu	Pro	His	Gly	His	Thr	Asp	Ala	Ala	Val	Lys	Ser	Pro	Phe
		195					200					205			
Leu	Lys	Lys	Cys	Gln	Glu	Ala	Gly	Leu	Leu	Thr	Glu	Leu	Phe	Glu	His
	210					215					220				
Ile	Leu	Glu	Asn	Met	Asp	Ser	Val	His	Gly	Arg	Leu	Val	Asp	Glu	Thr
225					230					235					240
Ala	Ser	Glu	Ser	Asp	Tyr	Glu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Asp	Cys

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<210> 46
<211> 244
<212> PRT
<213> Homo sapien
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$\langle 210 \rangle$	47
$\langle 211 \rangle$	14
$\langle 212 \rangle$	DNA

<213> Homo sapien

<400> 47

tttttttttt ttag

14

<210> 48

<211> 10

<212> DNA

<213> Homo sapien

<400> 48

cttcaacctc

10

<210> 49

<211> 496

<212> DNA

<213> Homo sapien

<400> 49

gcaccatgta	ccgagcactt	cggctcctcg	cgcgctcgcg	tcccctcgtg	cgggctccag	60
ccgcagcctt	agcttcgggt	cccggcttgg	gtggcgcggc	cgtgccctcg	ttttggcctc	120
cgaacgcggc	tcgaatggca	agccaaaatt	ccttccggat	agaatatgat	acctttgggtg	180
aactaaaggt	gccaaatgat	aagtattatg	gcgcccagac	cgtgagatct	acgatgaact	240
ttaagattgg	aggtgtgaca	gaacgcatgc	caaccccagt	tattaaagct	tttggcatct	300
tgaagcgagc	ggccgctgaa	gtaaaccagg	attatgggtc	tgatccaaag	attgctaattg	360
caataatgaa	ggcagcagat	gaggtagctg	aaggtaaatt	aaatgatcat	tttcctctcg	420
tggtatggca	gactggatca	ggaactcaga	caaatatgaa	tgtaaataaa	gtcattagcc	480
aatagagcaa	ttgaaa					496

<210> 50

<211> 499

<212> DNA

<213> Homo sapien

<400> 50

agaaaaagtc	tatgtttgca	gaaatacaga	tccaagacaa	agacaggatg	ggcactgctg	60
gaaaagtatt	taaatgcaaa	gcagctgtgc	tttggggagca	gaagcaaccc	ttctccattg	120
aggaaataga	agttgcccc	ccaaagacta	aagaagttcg	cattaagatt	ttggccacag	180
gaatctgtcg	cacagatgac	catgtgataa	aaggaacaat	ggtgtccaag	tttccagtga	240
ttgtggggca	tgaggcaact	gggattgtag	agagcattgg	agaaggagtg	actacagtga	300
aaccagggtg	caaagtcac	cctctctttc	tgccacaatg	tagagaatgc	aatgcttgct	360
gcaaccacga	tggaacact	tgcattagga	gcgatattac	tggtcgtgga	gtactggctg	420
atggcaccac	cagatttaca	tgcaagggcg	aaccagtcca	ccacttcatg	aacaccagta	480
catttaccga	gtacacagt					499

<210> 51

<211> 887

<212> DNA

<213> Homo sapien

<400> 51

gagtctgagc	agaaaggaaa	agcagccttg	gcagccacgt	tagagggaata	caaagccaca	60
gtggccagtg	accagataga	gatgaatcgc	ctgaaggctc	agctggagaa	tgaaaagcag	120
aaagtggcag	agctgtattc	tatccataac	tctggagaca	aatctgatat	tcaggacctc	180

ctggagagtg	tcaggctgga	caaagaaaaa	gcagagactt	tggctagtag	cttgcaggaa	240
gatctggctc	atacccga	tgatgccaat	cgattacagg	atgccattgc	taaggtagag	300
gatgaatacc	gagccttcca	agaagaagct	aagaaacaaa	ttgaagattt	gaatatgacg	360
ttagaaaaat	taagatcaga	cctggatgaa	aaagaaacag	aaaggagtga	catgaaagaa	420
accatctttg	aacttgaaga	tgaagtagaa	caacatcgtg	ctgtgaaact	tcatgacaac	480
ctcattat	ctgatctaga	gaatacagtt	aaaaaactcc	aggacaaaaa	gcacgacatg	540
gaaagagaaa	taaagacact	ccacagaaga	cttcgggaag	aatctgcgga	atggcggcag	600
tttcaggctg	atctccagac	tgcagtagtc	attgcaaatg	acattaaatc	tgaagcccaa	660
gaggagattg	gtgatctaaa	gcgccgggta	catgaggctc	aagaaaaaaa	tgagaaactc	720
acaaaagaat	tggaggaaat	aaagtcacgc	aagcaagagg	aggagcggag	cgggtataca	780
attacatgaa	tgccgttgag	agagatttgg	cagccttaag	gcagggaatg	ggactgagta	840
gaaggtcctc	gacttcctca	gagccaactc	ctacagtaaa	aaccctc		887

<210> 52

<211> 491

<212> DNA

<213> Homo sapien

<400> 52

ggcacgagct	tttccaaaaa	tcatgctgct	cctttctcta	aagttcttac	atthttataga	60
aaggaacctt	tcactcttga	ggcctactac	agctctcctc	aggatttgcc	ctatccagat	120
cctgctatag	ctcagttttc	agttcagaaa	gtcactcctc	agtctgatgg	ctccagttca	180
aaagtgaag	tcaaagtctg	agtaaagtgc	catggcattt	tcagtgtgtc	cagtgcattc	240
ttagtggagg	ttcacaagtc	tgaggaaaat	gaggagccaa	tggaaacaga	tcagaatgca	300
aaggaggaag	agaagatgca	agtggaccag	gaggaaccac	atggtgaaga	gcaacagcag	360
cagacaccag	gcagaaaata	aggcagagtc	tgaagaaatg	gagacctctc	aagctggatc	420
caaggataaa	aagatggacc	aaccacccca	agccaagaag	gcaaaagtga	agaccagtac	480
tgtggacctg	g					491

<210> 53

<211> 787

<212> DNA

<213> Homo sapien

<400> 53

aagcagttga	gtaggcagaa	aaaagaacct	cttcattaag	gattaaaatg	tataggccag	60
cacgtgtaac	ttcgacttca	agattttctga	atccatatgt	agtatgtttc	attgtcgtcg	120
caggggtagt	gatcctggca	gtcaccatag	ctctacttgt	ttacttttta	gcttttgatc	180
aaaaatctta	ctttttatagg	agcagttttc	aactcctaaa	tgttgaatat	aatagtcagt	240
taaattcacc	agctacacag	gaatacagga	ctttgagtgg	aagaattgaa	tctctgatta	300
ctaaaacatt	caaagaatca	aattttaagaa	atcagttcat	cagagctcat	gttgccaaac	360
tgaggcaaga	tggtagtggg	gtgagagcgg	atggtgtcat	gaaatttcaa	ttcactagaa	420
ataacaatgg	agcatcaatg	aaaagcagaa	ttgagtctgt	tttacgacaa	atgctgaata	480
actctggaaa	cctggaaata	aacccttcaa	ctgagataac	atcacttact	gaccaggctg	540
cagcaaattg	gcttattaat	gaatgtgggg	ccggtccaga	cctaataaca	ttgtctgagc	600
agagaatcct	tggaggcact	gaggctgagg	agggaagctg	gccgtggcaa	gtcagtctgc	660
ggctcaataa	tgcccaccac	tgtggaggca	gcctgatcaa	taacatgtgg	atcctgacag	720
cagctcactg	cttcagaagc	aactctaata	ctcgtgactg	gattgccacg	tctgggtattt	780
ccacaac						787

<210> 54

<211> 386

<212> DNA

<213> Homo sapien

<400> 54

ggcattttca	gtgtgtccag	tgcattcttta	gtggagggttc	acaagtctga	ggaaaatgag	60
gagccaatgg	aaacagatca	gaatgcaaag	gaggaagaga	agatgcaagt	ggaccaggag	120
gaaccacatg	ttgaagagca	acagcagcag	acaccagcag	aaaataaggc	agagtctgaa	180
gaaatggaga	cctctcaagc	tggatccaag	gataaaaaga	tggaccaacc	acccaagcc	240
aagaaggcaa	aagtgaagac	cagtactgtg	gacctgccaa	tcgagaatca	gctattatgg	300
cagatagaca	gagagatgct	caacttgtac	attgaaaatg	agggttaagat	gatcatgcag	360
gataaactgg	agaaggagcg	gaatga				386

<210> 55

<211> 1462

<212> DNA

<213> Homo sapien

<400> 55

aagcagttga	gtaggcagaa	aaaagaacct	cttcattaag	gattaaaatg	tataggccag	60
cacgtgtaac	ttcgacttca	agattttctga	atccatatgt	agtatgtttc	attgtcgtcg	120
caggggtagt	gaccttgga	gtcaccatag	ctctacttgt	ttacttttta	gcttttgatc	180
aaaaatctta	cttttatagg	agcagttttc	aactcctaaa	tgttgaatat	aatagtcagt	240
taaattcacc	agctacacag	gaatacagga	ctttgagtgg	aagaattgaa	tctctgatta	300
ctaaaacatt	caaagaatca	aatttaagaa	atcagttcat	cagagctcat	gttgccaaac	360
tgaggcaaga	tggtagtgg	gtgagagcgg	atgttgtcat	gaaatttcaa	ttcactagaa	420
ataacaatgg	agcatcaatg	aaaagcagaa	ttgagtctgt	tttacgacaa	atgctgaata	480
actctggaaa	cctggaaata	aacccttcaa	ctgagataac	atcacttact	gaccaggctg	540
cagcaaattg	gcttattaat	gaatgtgggg	ccggtccaga	cctaataaca	ttgtctgagc	600
agagaatcct	tgagggcact	gaggctgagg	agggaagctg	gccgtggcaa	gtcagtcctgc	660
ggctcaataa	tgcccaccac	tgtggaggca	gcctgatcaa	taacatgtgg	atcctgacag	720
cagctcactg	cttcagaagc	aactctaate	ctcgtgactg	gattgccacg	tctggatatt	780
ccacaacatt	tcctaaacta	agaatgagag	taagaaatat	tttaattcat	aacaattata	840
aatctgcaac	tcattgaaaat	gacattgcac	ttgtgagact	tgagaacagt	gtcaccttta	900
ccaaagatat	ccatagtgtg	tgtctcccag	ctgctaccca	gaatattcca	cctggctcta	960
ctgcttatgt	aacaggatgg	ggcgtcgaag	aatatgctgg	ccacacagtt	ccagagctaa	1020
ggcaaggaca	ggtcagaata	ataagtaatg	atgtatgtaa	tgcaccacat	agttataatg	1080
gagccatctt	gtctggaatg	ctgtgtgctg	gagtacctca	agggtggagt	gacgcagtgc	1140
agggtgactc	tggtggccca	ctagtacaag	aagactcacg	gcggctttgg	tttattgtgg	1200
ggatagtaag	ctgggggagat	cagtgtggcc	tgccggataa	gccaggagt	tatactcgag	1260
tgacagcata	cattgactgg	attaggcaac	aaactgggat	ctagtgaac	aagtgcattc	1320
ctgttgcaaa	gtctgtatgc	aggtgtgcct	gtcttaaat	ccaaagcttt	acatttcaac	1380
tgaaaaagaa	actagaaatg	tcctaattta	acatcttggt	acataaatat	ggtttaacaa	1440
aaaaaaaaaa	aaaaaactcg	ag				1462

<210> 56

<211> 159

<212> PRT

<213> Homo sapien

<400> 56

Thr	Met	Tyr	Arg	Ala	Leu	Arg	Leu	Leu	Ala	Arg	Ser	Arg	Pro	Leu	Val
1				5					10					15	
Arg	Ala	Pro	Ala	Ala	Ala	Leu	Ala	Ser	Ala	Pro	Gly	Leu	Gly	Gly	Ala
			20					25					30		
Ala	Val	Pro	Ser	Phe	Trp	Pro	Pro	Asn	Ala	Ala	Arg	Met	Ala	Ser	Gln
		35					40					45			

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<210> 57
<211> 165
<212> PRT
<213> Homo sapien
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[illegible]

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<210> 58
<211> 259
<212> PRT
<213> Homo sapien
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Glu	Ser	Glu	Gln	Lys	Gly	Lys	Ala	Ala	Leu	Ala	Ala	Thr	Leu	Glu	Glu
1				5					10					15	
Tyr	Lys	Ala	Thr	Val	Ala	Ser	Asp	Gln	Ile	Glu	Met	Asn	Arg	Leu	Lys
			20					25					30		

Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
 35 40 45
 His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
 50 55 60
 Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
 65 70 75 80
 Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
 85 90 95
 Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
 100 105 110
 Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
 115 120 125
 Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
 130 135 140
 Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
 145 150 155 160
 Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
 165 170 175
 Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
 180 185 190
 Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
 195 200 205
 Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
 210 215 220
 Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
 225 230 235 240
 Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
 245 250 255
 Gly Gly Tyr

<210> 59
 <211> 125
 <212> PRT
 <213> Homo sapien

<400> 59
 Gly Thr Ser Phe Ser Lys Asn His Ala Ala Pro Phe Ser Lys Val Leu
 1 5 10 15
 Thr Phe Tyr Arg Lys Glu Pro Phe Thr Leu Glu Ala Tyr Tyr Ser Ser
 20 25 30
 Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
 35 40 45
 Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
 50 55 60
 Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
 65 70 75 80
 Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr
 85 90 95
 Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
 100 105 110
 Pro His Val Glu Glu Gln Gln Gln Gln Thr Pro Gly Arg
 115 120 125

<210> 60
 <211> 246
 <212> PRT
 <213> Homo sapien

<400> 60

Met	Tyr	Arg	Pro	Ala	Arg	Val	Thr	Ser	Thr	Ser	Arg	Phe	Leu	Asn	Pro
1				5					10					15	
Tyr	Val	Val	Cys	Phe	Ile	Val	Val	Ala	Gly	Val	Val	Ile	Leu	Ala	Val
			20					25					30		
Thr	Ile	Ala	Leu	Leu	Val	Tyr	Phe	Leu	Ala	Phe	Asp	Gln	Lys	Ser	Tyr
		35					40					45			
Phe	Tyr	Arg	Ser	Ser	Phe	Gln	Leu	Leu	Asn	Val	Glu	Tyr	Asn	Ser	Gln
	50					55					60				
Leu	Asn	Ser	Pro	Ala	Thr	Gln	Glu	Tyr	Arg	Thr	Leu	Ser	Gly	Arg	Ile
65					70					75					80
Glu	Ser	Leu	Ile	Thr	Lys	Thr	Phe	Lys	Glu	Ser	Asn	Leu	Arg	Asn	Gln
				85					90					95	
Phe	Ile	Arg	Ala	His	Val	Ala	Lys	Leu	Arg	Gln	Asp	Gly	Ser	Gly	Val
			100					105						110	
Arg	Ala	Asp	Val	Val	Met	Lys	Phe	Gln	Phe	Thr	Arg	Asn	Asn	Asn	Gly
		115					120					125			
Ala	Ser	Met	Lys	Ser	Arg	Ile	Glu	Ser	Val	Leu	Arg	Gln	Met	Leu	Asn
		130				135					140				
Asn	Ser	Gly	Asn	Leu	Glu	Ile	Asn	Pro	Ser	Thr	Glu	Ile	Thr	Ser	Leu
145					150					155					160
Thr	Asp	Gln	Ala	Ala	Ala	Asn	Trp	Leu	Ile	Asn	Glu	Cys	Gly	Ala	Gly
				165					170					175	
Pro	Asp	Leu	Ile	Thr	Leu	Ser	Glu	Gln	Arg	Ile	Leu	Gly	Gly	Thr	Glu
			180					185					190		
Ala	Glu	Glu	Gly	Ser	Trp	Pro	Trp	Gln	Val	Ser	Leu	Arg	Leu	Asn	Asn
		195					200					205			
Ala	His	His	Cys	Gly	Gly	Ser	Leu	Ile	Asn	Asn	Met	Trp	Ile	Leu	Thr
		210				215					220				
Ala	Ala	His	Cys	Phe	Arg	Ser	Asn	Ser	Asn	Pro	Arg	Asp	Trp	Ile	Ala
225					230					235					240
Thr	Ser	Gly	Ile	Ser	Thr										
				245											

<210> 61
 <211> 128
 <212> PRT
 <213> Homo sapien

<400> 61

Gly	Ile	Phe	Ser	Val	Ser	Ser	Ala	Ser	Leu	Val	Glu	Val	His	Lys	Ser
1				5					10					15	
Glu	Glu	Asn	Glu	Glu	Pro	Met	Glu	Thr	Asp	Gln	Asn	Ala	Lys	Glu	Glu
			20					25					30		
Glu	Lys	Met	Gln	Val	Asp	Gln	Glu	Glu	Pro	His	Val	Glu	Glu	Gln	Gln
		35					40					45			
Gln	Gln	Thr	Pro	Ala	Glu	Asn	Lys	Ala	Glu	Ser	Glu	Glu	Met	Glu	Thr
	50					55					60				
Ser	Gln	Ala	Gly	Ser	Lys	Asp	Lys	Lys	Met	Asp	Gln	Pro	Pro	Gln	Ala


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<210> 62
<211> 418
<212> PRT
<213> Homo sapien
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	<400> 62														
Met 1	Tyr	Arg	Pro	Ala	Arg	Val	Thr	Ser	Thr	Ser	Arg	Phe	Leu	Asn	Pro
				5					10					15	
Tyr	Val	Val	Cys	Phe	Ile	Val	Val	Ala	Gly	Val	Val	Ile	Leu	Ala	Val
			20					25					30		
Thr	Ile	Ala	Leu	Leu	Val	Tyr	Phe	Leu	Ala	Phe	Asp	Gln	Lys	Ser	Tyr
		35					40					45			
Phe	Tyr	Arg	Ser	Ser	Phe	Gln	Leu	Leu	Asn	Val	Glu	Tyr	Asn	Ser	Gln
	50					55					60				
Leu	Asn	Ser	Pro	Ala	Thr	Gln	Glu	Tyr	Arg	Thr	Leu	Ser	Gly	Arg	Ile
65					70					75					80
Glu	Ser	Leu	Ile	Thr	Lys	Thr	Phe	Lys	Glu	Ser	Asn	Leu	Arg	Asn	Gln
				85					90					95	
Phe	Ile	Arg	Ala	His	Val	Ala	Lys	Leu	Arg	Gln	Asp	Gly	Ser	Gly	Val
			100					105					110		
Arg	Ala	Asp	Val	Val	Met	Lys	Phe	Gln	Phe	Thr	Arg	Asn	Asn	Asn	Gly
		115					120					125			
Ala	Ser	Met	Lys	Ser	Arg	Ile	Glu	Ser	Val	Leu	Arg	Gln	Met	Leu	Asn
	130					135					140				
Asn	Ser	Gly	Asn	Leu	Glu	Ile	Asn	Pro	Ser	Thr	Glu	Ile	Thr	Ser	Leu
145					150					155					160
Thr	Asp	Gln	Ala	Ala	Ala	Asn	Trp	Leu	Ile	Asn	Glu	Cys	Gly	Ala	Gly
				165					170					175	
Pro	Asp	Leu	Ile	Thr	Leu	Ser	Glu	Gln	Arg	Ile	Leu	Gly	Gly	Thr	Glu
			180					185					190		
Ala	Glu	Glu	Gly	Ser	Trp	Pro	Trp	Gln	Val	Ser	Leu	Arg	Leu	Asn	Asn
		195					200					205			
Ala	His	His	Cys	Gly	Gly	Ser	Leu	Ile	Asn	Asn	Met	Trp	Ile	Leu	Thr
	210					215					220				
Ala	Ala	His	Cys	Phe	Arg	Ser	Asn	Ser	Asn	Pro	Arg	Asp	Trp	Ile	Ala
225					230					235					240
Thr	Ser	Gly	Ile	Ser	Thr	Thr	Phe	Pro	Lys	Leu	Arg	Met	Arg	Val	Arg
				245					250					255	
Asn	Ile	Leu	Ile	His	Asn	Asn	Tyr	Lys	Ser	Ala	Thr	His	Glu	Asn	Asp
			260					265					270		
Ile	Ala	Leu	Val	Arg	Leu	Glu	Asn	Ser	Val	Thr	Phe	Thr	Lys	Asp	Ile
		275					280					285			
His	Ser	Val	Cys	Leu	Pro	Ala	Ala	Thr	Gln	Asn	Ile	Pro	Pro	Gly	Ser
	290					295					300				
Thr	Ala	Tyr	Val	Thr	Gly	Trp	Gly	Ala	Gln	Glu	Tyr	Ala	Gly	His	Thr
305					310						315				320

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<210> 63
<211> 776
<212> DNA
<213> Homo sapien
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<210> 64
<211> 160
<212> DNA
<213> Homo sapien
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<210> 65
<211> 72
<212> PRT
<213> Homo sapien
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      <400> 65
Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser Ser Ile
 1          5          10          15
Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Gly Val

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	20		25		30
Ala	Ser Gly	Ser Leu Val	Ala Thr Leu Gln Ser	Leu Gly Ala Thr Gly	
	35		40		45
Leu	Ser Gly	Leu Thr Lys Phe	Ile Leu Gly Ser	Ile Gly Ser Ala Ile	
	50		55		60
Ala	Ala Val	Ile Ala Arg Phe Tyr			
65		70			

<210> 66
 <211> 2581
 <212> DNA
 <213> Homo sapien

<400> 66

ctttcaaccc	gcgctcgccg	gctccagccc	cgcgcgcccc	caccccttgc	cctcccggcg	60
gctccgcagg	gtgaggtggc	tttgaccccc	ggttgccccg	ccagcacgac	cgaggaggtg	120
gctggacagc	tggaggatga	acggagaagc	cgactgcccc	acagacctgg	aaatggccgc	180
ccccaaaggc	caagaccgtt	ggtcccagga	agacatgctg	actttgctgg	aatgcatgaa	240
gaacaacctt	ccatccaatg	acagctccaa	gttcaaaaacc	accgaatcac	acatggactg	300
ggaaaaagta	gcattttaaag	actttttctgg	agacatgtgc	aagctcaaata	gggtggagat	360
ttctaatagag	gtgaggaagt	tccgtacatt	gacagaattg	atcctcgatg	ctcaggaaca	420
tgttaaaaat	ccttacaaaag	gcaaaaaact	caagaaacac	ccagacttcc	caaagaagcc	480
cctgaccctt	tatttccgct	tcttcatgga	gaagcggggc	aagtatgcga	aactccaccc	540
tgagatgagc	aacctggacc	taaccaagat	tctgtccaag	aaatacaagg	agcttccgga	600
gaagaagaag	atgaaatata	ttcaggactt	ccagagagag	aaacaggagt	tcgagcgaaa	660
cctggcccga	ttcagggagg	atcaccccga	cctaateccag	aatgccaaga	aatcggacat	720
cccagagaag	cccaaaaccc	cccagcagct	gtggtacacc	cacgagaaga	aggtgtatct	780
caaagtgcgg	ccagatgcca	ctacgaagga	ggtgaaggac	tccctgggga	agcagtggtc	840
tcagctctcg	gacaaaaaga	ggctgaaatg	gattcataag	gccctggagc	agcggaagga	900
gtacgaggag	atcatgagag	actatatcca	gaagcaccca	gagctgaaca	tcagtgagga	960
gggtatcacc	aagtccaccc	tcaccaaggc	cgaacgccag	ctcaaggaca	agtttgacgg	1020
gcgaccaccc	aagccacctc	cgaacagcta	ctcgctgtac	tgcgcagagc	tcattggccaa	1080
catgaaggac	gtgcccagca	cagagcgcat	ggtgctgtgc	agccagcagt	ggaagctgct	1140
gtcccagaag	gagaaggacg	cctatcacaa	gaagtgtgat	cagaaaaaga	aagattacga	1200
ggtggagctg	ctccgtttcc	tcgagagcct	gcctgaggag	gagcagcagc	gggtcttggg	1260
ggaagagaag	atgctgaaca	tcaacaagaa	gcaggccacc	agccccgcct	ccaagaagcc	1320
agcccaggaa	gggggcaagg	gcggctccga	gaagcccagg	cggcccgtgt	cggccatggt	1380
catcttctcg	gaggagaaac	ggcggcagct	gcaggaggag	cggcctgagc	tctccgagag	1440
cgagctgacc	cgcttctggg	cccgaatgtg	gaacgacctg	tctgagaaga	agaaggccaa	1500
gtacaaggcc	cgagaggcgg	cgctcaaggc	tcagtcggag	aggaagcccg	gcggggagcg	1560
cgaggaacgg	ggcaagctgc	ccgagtcccc	caaaagagct	gaggagatct	ggcaacagag	1620
cgttatcggc	gactacctgg	cccgttccaa	gaatgaccgg	gtgaaggcct	tgaaagccat	1680
ggaaatgacc	tggaataaca	tggaaaaagaa	ggagaaactg	atgtggatta	agaaggcagc	1740
cgaagaccaa	aagcgatatg	agagagagct	gagtggagatg	cgggcacctc	cagctgctac	1800
aaattcttcc	aagaagatga	aattccaggg	agaacccaag	aagcctccca	tgaacggtta	1860
ccagaagtcc	tcccaggagc	tgctgtccaa	tggggagctg	aaccacctgc	cgctgaagga	1920
gcgcatgggtg	gagatcggca	gtcgctggca	gcgcatctcc	cagagccaga	aggagcacta	1980
caaaaagctg	gccgaggagc	agcaaaaagca	gtacaagggtg	cacctggacc	tctgggttaa	2040
gagcctgtct	ccccaggacc	gtgcagcata	taaagagtac	atctccaata	aacgtaagag	2100
catgaccaag	ctgcgaggcc	caaaccccaa	atccagccgg	actactctgc	agtccaagtc	2160
ggagtccgag	gaggatgatg	aagaggatga	ggatgacgag	gacgaggatg	aagaagagga	2220
agatgatgag	aatggggact	cctctgaaga	tggcggcgac	tcctctgagt	ccagcagcga	2280
ggacgagagc	gaggatgggg	atgagaatga	agaggatgac	gaggacgaag	acgacgacga	2340
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<210> 67
<211> 764
<212> PRT
<213> Homo sapien
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	<400> 67														
Met 1	Asn	Gly	Glu	Ala 5	Asp	Cys	Pro	Thr	Asp 10	Leu	Glu	Met	Ala	Ala 15	Pro
Lys	Gly	Gln	Asp 20	Arg	Trp	Ser	Gln	Glu 25	Asp	Met	Leu	Thr	Leu 30	Leu	Glu
Cys	Met	Lys 35	Asn	Asn	Leu	Pro	Ser 40	Asn	Asp	Ser	Ser	Lys 45	Phe	Lys	Thr
Thr	Glu 50	Ser	His	Met	Asp	Trp 55	Glu	Lys	Val	Ala	Phe 60	Lys	Asp	Phe	Ser
Gly 65	Asp	Met	Cys	Lys	Leu 70	Lys	Trp	Val	Glu	Ile	Ser 75	Asn	Glu	Val	Arg 80
Lys	Phe	Arg	Thr	Leu 85	Thr	Glu	Leu	Ile	Leu 90	Asp	Ala	Gln	Glu 95	His	Val
Lys	Asn	Pro	Tyr 100	Lys	Gly	Lys	Lys	Leu 105	Lys	Lys	His	Pro	Asp 110	Phe	Pro
Lys	Lys	Pro	Leu	Thr	Pro	Tyr	Phe 120	Arg	Phe	Phe	Met	Glu 125	Lys	Arg	Ala
Lys	Tyr 130	Ala	Lys	Leu	His	Pro 135	Glu	Met	Ser	Asn	Leu 140	Asp	Leu	Thr	Lys
Ile 145	Leu	Ser	Lys	Lys	Tyr 150	Lys	Glu	Leu	Pro	Glu	Lys 155	Lys	Lys	Met	Lys 160
Tyr	Ile	Gln	Asp	Phe 165	Gln	Arg	Glu	Lys	Gln 170	Glu	Phe	Glu	Arg	Asn 175	Leu
Ala	Arg	Phe	Arg	Glu 180	Asp	His	Pro	Asp 185	Leu	Ile	Gln	Asn	Ala 190	Lys	Lys
Ser	Asp	Ile 195	Pro	Glu	Lys	Pro	Lys 200	Thr	Pro	Gln	Gln	Leu 205	Trp	Tyr	Thr
His	Glu 210	Lys	Lys	Val	Tyr	Leu 215	Lys	Val	Arg	Pro	Asp 220	Ala	Thr	Thr	Lys
Glu 225	Val	Lys	Asp	Ser	Leu 230	Gly	Lys	Gln	Trp	Ser	Gln 235	Leu	Ser	Asp	Lys 240
Lys	Arg	Leu	Lys	Trp 245	Ile	His	Lys	Ala	Leu 250	Glu	Gln	Arg	Lys	Glu 255	Tyr
Glu	Glu	Ile	Met	Arg 260	Asp	Tyr	Ile	Gln 265	Lys	His	Pro	Glu 270	Leu	Asn	Ile
Ser	Glu	Glu 275	Gly	Ile	Thr	Lys	Ser 280	Thr	Leu	Thr	Lys	Ala 285	Glu	Arg	Gln
Leu	Lys 290	Asp	Lys	Phe	Asp	Gly 295	Arg	Pro	Thr	Lys	Pro 300	Pro	Pro	Asn	Ser
Tyr 305	Ser	Leu	Tyr	Cys	Ala 310	Glu	Leu	Met	Ala	Asn	Met 315	Lys	Asp	Val	Pro 320
Ser	Thr	Glu	Arg	Met 325	Val	Leu	Cys	Ser	Gln 330	Gln	Trp	Lys	Leu	Leu 335	Ser
Gln	Lys	Glu	Lys	Asp	Ala	Tyr	His	Lys	Lys	Cys	Asp	Gln	Lys	Lys	Lys

			340					345				350					
Asp	Tyr	Glu	Val	Glu	Leu	Leu	Arg	Phe	Leu	Glu	Ser	Leu	Pro	Glu	Glu		
		355					360					365					
Glu	Gln	Gln	Arg	Val	Leu	Gly	Glu	Glu	Lys	Met	Leu	Asn	Ile	Asn	Lys		
	370					375					380						
Lys	Gln	Ala	Thr	Ser	Pro	Ala	Ser	Lys	Lys	Pro	Ala	Gln	Glu	Gly	Gly		
385					390					395					400		
Lys	Gly	Gly	Ser	Glu	Lys	Pro	Lys	Arg	Pro	Val	Ser	Ala	Met	Phe	Ile		
				405				410						415			
Phe	Ser	Glu	Glu	Lys	Arg	Arg	Gln	Leu	Gln	Glu	Glu	Arg	Pro	Glu	Leu		
			420				425						430				
Ser	Glu	Ser	Glu	Leu	Thr	Arg	Leu	Leu	Ala	Arg	Met	Trp	Asn	Asp	Leu		
		435					440					445					
Ser	Glu	Lys	Lys	Lys	Ala	Lys	Tyr	Lys	Ala	Arg	Glu	Ala	Ala	Leu	Lys		
	450					455					460						
Ala	Gln	Ser	Glu	Arg	Lys	Pro	Gly	Gly	Glu	Arg	Glu	Glu	Arg	Gly	Lys		
465					470					475					480		
Leu	Pro	Glu	Ser	Pro	Lys	Arg	Ala	Glu	Glu	Ile	Trp	Gln	Gln	Ser	Val		
				485				490						495			
Ile	Gly	Asp	Tyr	Leu	Ala	Arg	Phe	Lys	Asn	Asp	Arg	Val	Lys	Ala	Leu		
		500					505						510				
Lys	Ala	Met	Glu	Met	Thr	Trp	Asn	Asn	Met	Glu	Lys	Lys	Glu	Lys	Leu		
	515						520					525					
Met	Trp	Ile	Lys	Lys	Ala	Ala	Glu	Asp	Gln	Lys	Arg	Tyr	Glu	Arg	Glu		
	530				535						540						
Leu	Ser	Glu	Met	Arg	Ala	Pro	Pro	Ala	Ala	Thr	Asn	Ser	Ser	Lys	Lys		
545					550					555					560		
Met	Lys	Phe	Gln	Gly	Glu	Pro	Lys	Lys	Pro	Pro	Met	Asn	Gly	Tyr	Gln		
				565				570						575			
Lys	Phe	Ser	Gln	Glu	Leu	Leu	Ser	Asn	Gly	Glu	Leu	Asn	His	Leu	Pro		
			580				585						590				
Leu	Lys	Glu	Arg	Met	Val	Glu	Ile	Gly	Ser	Arg	Trp	Gln	Arg	Ile	Ser		
	595					600						605					
Gln	Ser	Gln	Lys	Glu	His	Tyr	Lys	Lys	Leu	Ala	Glu	Glu	Gln	Gln	Lys		
	610					615					620						
Gln	Tyr	Lys	Val	His	Leu	Asp	Leu	Trp	Val	Lys	Ser	Leu	Ser	Pro	Gln		
625					630					635					640		
Asp	Arg	Ala	Ala	Tyr	Lys	Glu	Tyr	Ile	Ser	Asn	Lys	Arg	Lys	Ser	Met		
				645				650						655			
Thr	Lys	Leu	Arg	Gly	Pro	Asn	Pro	Lys	Ser	Ser	Arg	Thr	Thr	Leu	Gln		
			660				665						670				
Ser	Lys	Ser	Glu	Ser	Glu	Glu	Asp	Asp	Glu	Glu	Asp	Glu	Asp	Asp	Glu		
		675					680					685					
Asp	Glu	Asp	Glu	Glu	Glu	Glu	Asp	Asp	Glu	Asn	Gly	Asp	Ser	Ser	Glu		
	690				695					700							
Asp	Gly	Gly	Asp	Ser	Ser	Glu	Ser	Ser	Ser	Glu	Asp	Glu	Ser	Glu	Asp		
705					710					715					720		
Gly	Asp	Glu	Asn	Glu	Glu	Asp	Asp	Glu	Asp	Glu	Asp	Asp	Asp	Glu	Asp		
				725				730						735			
Asp	Asp	Glu	Asp	Glu	Asp	Asn	Glu	Ser	Glu	Gly	Ser	Ser	Ser	Ser	Ser		
		740					745						750				
Ser	Ser	Leu	Gly	Asp	Ser	Ser	Asp	Phe	Asp	Ser	Asn						
		755					760										

<210> 68
 <211> 434
 <212> DNA
 <213> Homo sapien

<400> 68
 ctaagatgct ggatgctgaa gacatcgctg gaactgcccg gccagatgag aaagccatta 60
 tgacttatgt gtctagcttc tatcatgcct tctctggagc ccagaaggca gaaacagcag 120
 ccaatcgcat ctgcaaagtg ttggcgggtca atcaagagaa cgagcagctt atggaagact 180
 atgagaagct ggccagtgat ctgttggagt ggatccgccc caccatccca tggctggaga 240
 atcgggtgcc tgagaacacc atgcatgcc a tgcagcagaa gctggaggac ttccgagact 300
 atagacgcct gcacaagccg cccaagggtgc aggagaagtg ccagctggag atcaacttta 360
 acacgctgca gaccaaactg cggtcagca accggcctgc cttcatgccc tccgagggca 420
 ggatgggtctc ggat 434

<210> 69
 <211> 244
 <212> DNA
 <213> Homo sapien

<400> 69
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 aactgcgga aggcgcgagg gtccctctgcc taggaaaacc agagaccttt gttcacttgt 120
 ttatgtgctg accttccctc cactattgtc ctgtgacctt gccaaatccc cctttgtgag 180
 aaacacccaa gaatgatcaa taaaaaataa attaatttag gaaaaaaaaa aaaaaaaact 240
 cgag 244

<210> 70
 <211> 437
 <212> DNA
 <213> Homo sapien

<400> 70
 ctgggacggg agcgtccagc gggactcgaa ccccagatgt gaaggcgttt ctggaaagtc 60
 cttgggtccct ggatccagcg tcggccagcc cagagcccgt gccgcacatc cttgcgtcct 120
 ccaggcagtg ggaccccgcg agctgcacgt ccctgggcac ggacaagtgt gaggcactgt 180
 tggggctgtg ccagggtgcg ggtgggctgc cccctttctc agaaccttcc agcctggtgc 240
 cgtggccccc aggcgggagt cttcctaagg ctgtgaggcc acccctgtcc tggcctccgt 300
 tctcgcagca gcagaccttg cccgtgatga gcggggaggc ccttggtgctg ctggggccagg 360
 ctggttccct ggccatgggg gctgcacctc tgggggagcc agccaaggag gaccccatgc 420
 tggcgcagga agccggg 437

<210> 71
 <211> 271
 <212> DNA
 <213> Homo sapien

<400> 71
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 aagagatggc tctcttcagt gccagcttc catacattaa cccgatcatc ccctttactg 120
 gaccaatcca aggagggtg caggaggagc ttcagggtgac cctccagggg actaccgaga 180
 gttttgcaca aaagtgtgtg gtgaactttt cagaacagct tcaatggaga tgacttggcc 240
 ttccacttca accccggtta tgaggaagga g 271

<210> 72
 <211> 290
 <212> DNA
 <213> Homo sapien

<400> 72
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 ctggtgccct ctctgctgc gaggactcgg cccagggctc gggcccgccc aaggccccta 120
 cgggtggccga ggggtcccagc tcctgccttc ggcggaacgt gatcagcgag agggagcgca 180
 ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc 240
 ggcgggagga catggcctcg gtcctggaga tgtctgttgc aattcctgcg 290

<210> 73
 <211> 144
 <212> PRT
 <213> Homo sapien

<400> 73
 Lys Met Leu Asp Ala Glu Asp Ile Val Gly Thr Ala Arg Pro Asp Glu
 1 5 10 15
 Lys Ala Ile Met Thr Tyr Val Ser Ser Phe Tyr His Ala Phe Ser Gly
 20 25 30
 Ala Gln Lys Ala Glu Thr Ala Ala Asn Arg Ile Cys Lys Val Leu Ala
 35 40 45
 Val Asn Gln Glu Asn Glu Gln Leu Met Glu Asp Tyr Glu Lys Leu Ala
 50 55 60
 Ser Asp Leu Leu Glu Trp Ile Arg Arg Thr Ile Pro Trp Leu Glu Asn
 65 70 75 80
 Arg Val Pro Glu Asn Thr Met His Ala Met Gln Gln Lys Leu Glu Asp
 85 90 95
 Phe Arg Asp Tyr Arg Arg Leu His Lys Pro Pro Lys Val Gln Glu Lys
 100 105 110
 Cys Gln Leu Glu Ile Asn Phe Asn Thr Leu Gln Thr Lys Leu Arg Leu
 115 120 125
 Ser Asn Arg Pro Ala Phe Met Pro Ser Glu Gly Arg Met Val Ser Asp
 130 135 140

<210> 74
 <211> 64
 <212> PRT
 <213> Homo sapien

<400> 74
 Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
 1 5 10 15
 Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
 20 25 30
 Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
 35 40 45
 Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
 50 55 60

<210> 75
 <211> 145

<212> PRT

<213> Homo sapien

<400> 75

Gly	Thr	Gly	Ala	Ser	Ser	Gly	Thr	Arg	Thr	Pro	Asp	Val	Lys	Ala	Phe
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Leu	Glu	Ser	Pro	Trp	Ser	Leu	Asp	Pro	Ala	Ser	Ala	Ser	Pro	Glu	Pro
			20					25					30		
Val	Pro	His	Ile	Leu	Ala	Ser	Ser	Arg	Gln	Trp	Asp	Pro	Ala	Ser	Cys
		35					40					45			
Thr	Ser	Leu	Gly	Thr	Asp	Lys	Cys	Glu	Ala	Leu	Leu	Gly	Leu	Cys	Gln
		50				55					60				
Val	Arg	Gly	Gly	Leu	Pro	Pro	Phe	Ser	Glu	Pro	Ser	Ser	Leu	Val	Pro
65					70					75					80
Trp	Pro	Pro	Gly	Arg	Ser	Leu	Pro	Lys	Ala	Val	Arg	Pro	Pro	Leu	Ser
				85					90					95	
Trp	Pro	Pro	Phe	Ser	Gln	Gln	Gln	Thr	Leu	Pro	Val	Met	Ser	Gly	Glu
			100					105					110		
Ala	Leu	Gly	Trp	Leu	Gly	Gln	Ala	Gly	Ser	Leu	Ala	Met	Gly	Ala	Ala
		115				120						125			
Pro	Leu	Gly	Glu	Pro	Ala	Lys	Glu	Asp	Pro	Met	Leu	Ala	Gln	Glu	Ala
	130					135					140				
Gly															
145															

<210> 76

<211> 69

<212> PRT

<213> Homo sapien

<400> 76

Ala	Glu	Phe	Cys	Arg	Pro	Pro	Ser	Ser	Glu	Glu	Glu	Ser	Ile	Gly	Ser
1				5					10					15	
Pro	Glu	Ile	Glu	Glu	Met	Ala	Leu	Phe	Ser	Ala	Gln	Ser	Pro	Tyr	Ile
			20					25					30		
Asn	Pro	Ile	Ile	Pro	Phe	Thr	Gly	Pro	Ile	Gln	Gly	Gly	Leu	Gln	Glu
		35					40					45			
Gly	Leu	Gln	Val	Thr	Leu	Gln	Gly	Thr	Thr	Glu	Ser	Phe	Ala	Gln	Lys
	50					55					60				
Phe	Val	Val	Asn	Phe											
65															

<210> 77

<211> 96

<212> PRT

<213> Homo sapien

<400> 77

Glu	Pro	Tyr	Pro	Glu	Val	Ser	Arg	Ile	Pro	Thr	Val	Arg	Gly	Cys	Asn
1				5					10					15	
Gly	Ser	Leu	Ser	Gly	Ala	Leu	Ser	Cys	Cys	Glu	Asp	Ser	Ala	Gln	Gly
			20					25					30		
Ser	Gly	Pro	Pro	Lys	Ala	Pro	Thr	Val	Ala	Glu	Gly	Pro	Ser	Ser	Cys
		35					40					45			

Leu Arg Arg Asn Val Ile Ser Glu Arg Glu Arg Arg Lys Arg Met Ser
 50 55 60
 Leu Ser Cys Glu Arg Leu Arg Ala Leu Leu Pro Gln Phe Asp Gly Arg
 65 70 75 80
 Arg Glu Asp Met Ala Ser Val Leu Glu Met Ser Val Ala Ile Pro Ala
 85 90 95

<210> 78

<211> 2076

<212> DNA

<213> Homo sapien

<400> 78

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<210> 79

<211> 2790

<212> DNA

<213> Homo sapien

<400> 79

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<210> 80

<211> 1460

<212> DNA

<213> Homo sapien

<400> 80

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gatcaaaaat cttactttta taggagcagt tttcaactcc taaatgttga atataatagt      240
cagttaaatt caccagctac acaggaatac aggactttga gtggaagaat tgaatctctg      300
attactaaaa cattcaaaga atcaaattta agaatcagt tcatcagagc tcatgttgcc      360
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<210> 81

<211> 386

<212> PRT

<213> Homo sapien

<400> 81

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Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys Thr Lys Glu
      35             40             45
Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr Asp Asp His
      50             55             60
Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile Val Gly His
65             70             75             80
Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val Thr Thr Val
      85             90             95
Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln Cys Arg Glu
      100            105            110
Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile Arg Ser Asp
      115            120            125
Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg Phe Thr Cys
      130            135            140
Lys Gly Lys Pro Val His His Phe Met Asn Thr Ser Thr Phe Thr Glu
145            150            155            160
Tyr Thr Val Val Asp Glu Ser Ser Val Ala Lys Ile Asp Asp Ala Ala

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Pro	Pro	Glu	Lys	Val	Cys	Leu	Ile	Gly	Cys	Gly	Phe	Ser	Thr	Gly	Tyr
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Gly	Ala	Ala	Val	Lys	Thr	Gly	Lys	Val	Lys	Pro	Gly	Ser	Thr	Cys	Val
		195					200					205			
Val	Phe	Gly	Leu	Arg	Gly	Val	Gly	Leu	Ser	Val	Ile	Met	Gly	Cys	Lys
	210					215					220				
Ser	Ala	Gly	Ala	Ser	Arg	Ile	Ile	Gly	Ile	Asp	Leu	Asn	Lys	Asp	Lys
225					230					235					240
Phe	Glu	Lys	Ala	Met	Ala	Val	Gly	Ala	Thr	Glu	Cys	Ile	Ser	Pro	Lys
				245				250						255	
Asp	Ser	Thr	Lys	Pro	Ile	Ser	Glu	Val	Leu	Ser	Glu	Met	Thr	Gly	Asn
			260					265						270	
Asn	Val	Gly	Tyr	Thr	Phe	Glu	Val	Ile	Gly	His	Leu	Glu	Thr	Met	Ile
		275					280					285			
Asp	Ala	Leu	Ala	Ser	Cys	His	Met	Asn	Tyr	Gly	Thr	Ser	Val	Val	Val
	290					295					300				
Gly	Val	Pro	Pro	Ser	Ala	Lys	Met	Leu	Thr	Tyr	Asp	Pro	Met	Leu	Leu
305					310					315					320
Phe	Thr	Gly	Arg	Thr	Trp	Lys	Gly	Cys	Val	Phe	Gly	Gly	Leu	Lys	Ser
				325					330					335	
Arg	Asp	Asp	Val	Pro	Lys	Leu	Val	Thr	Glu	Phe	Leu	Ala	Lys	Lys	Phe
			340					345					350		
Asp	Leu	Asp	Gln	Leu	Ile	Thr	His	Val	Leu	Pro	Phe	Lys	Lys	Ile	Ser
		355				360						365			
Glu	Gly	Phe	Glu	Leu	Leu	Asn	Ser	Gly	Gln	Ser	Ile	Arg	Thr	Val	Leu
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Thr	Phe														
385															

<210> 82

<211> 418

<212> PRT

<213> Homo sapien

<400> 82

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			20					25					30		
Thr	Ile	Ala	Leu	Leu	Val	Tyr	Phe	Leu	Ala	Phe	Asp	Gln	Lys	Ser	Tyr
		35					40					45			
Phe	Tyr	Arg	Ser	Ser	Phe	Gln	Leu	Leu	Asn	Val	Glu	Tyr	Asn	Ser	Gln
	50					55					60				
Leu	Asn	Ser	Pro	Ala	Thr	Gln	Glu	Tyr	Arg	Thr	Leu	Ser	Gly	Arg	Ile
65					70					75					80
Glu	Ser	Leu	Ile	Thr	Lys	Thr	Phe	Lys	Glu	Ser	Asn	Leu	Arg	Asn	Gln
				85					90					95	
Phe	Ile	Arg	Ala	His	Val	Ala	Lys	Leu	Arg	Gln	Asp	Gly	Ser	Gly	Val
			100					105					110		
Arg	Ala	Asp	Val	Val	Met	Lys	Phe	Gln	Phe	Thr	Arg	Asn	Asn	Asn	Gly
		115					120					125			
Ala	Ser	Met	Lys	Ser	Arg	Ile	Glu	Ser	Val	Leu	Arg	Gln	Met	Leu	Asn
	130					135					140				

Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
 145 150 155 160
 Thr Asp Gln Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
 165 170 175
 Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
 180 185 190
 Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
 195 200 205
 Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
 210 215 220
 Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
 225 230 235 240
 Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
 245 250 255
 Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
 260 265 270
 Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
 275 280 285
 His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
 290 295 300
 Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
 305 310 315 320
 Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
 325 330 335
 Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
 340 345 350
 Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
 355 360 365
 Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
 370 375 380
 Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
 385 390 395 400
 Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
 405 410 415
 Gly Ile

<210> 83

<211> 418

<212> PRT

<213> Homo sapien

<400> 83

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 Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
 35 40 45
 Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
 50 55 60
 Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
 65 70 75 80
 Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln

85 90 95
 Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
 100 105 110
 Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
 115 120 125
 Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
 130 135 140
 Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
 145 150 155 160
 Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
 165 170 175
 Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
 180 185 190
 Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
 195 200 205
 Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
 210 215 220
 Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
 225 230 235 240
 Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
 245 250 255
 Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
 260 265 270
 Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
 275 280 285
 His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
 290 295 300
 Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
 305 310 315 320
 Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
 325 330 335
 Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
 340 345 350
 Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
 355 360 365
 Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
 370 375 380
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 405 410 415
 Gly Ile

<210> 84
 <211> 489
 <212> DNA
 <213> Homo sapien

<400> 84

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aattacagag gagtttcatg gcactaagtc aagatattca gaaaacaata aagaagacag	180
cacgtcggga gcagcttatg agagaagaag ctgaacagaa acgttttaaaa actgtacttg	240

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aagttctaa						489

<210> 85

<211> 304

<212> DNA

<213> Homo sapien

<400> 85

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agag						304

<210> 86

<211> 296

<212> DNA

<213> Homo sapien

<400> 86

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tccatatgtt	gtatgtttcc	ttgtcctccc	aggggttgtg	atcctggcag	tcccatagc	180
tctacttggt	tacttttttag	cttttgatca	aaaatcctac	ttttattgga	gcaattttcc	240
actcccaa	ggtgaatata	atagtcctgt	taattccccc	gcttcaccgg	gaattc	296

<210> 87

<211> 904

<212> DNA

<213> Homo sapien

<400> 87

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gtgcaggacg	gcattcttgc	accaaattga	atatttttagt	acagcaacat	tttgacttgg	240
cttcaactac	tattacaaat	attccaatga	aggaagaaca	gcatgctaac	acatctgcca	300
attatgatgt	ggagctactt	catcacaaag	atgcacatgt	agatttcctg	aaaagtgggtg	360
attcgcattc	aggtggcggc	agtcgagaag	gctcgtttta	agaaacaata	acattaaagt	420
ggtgtacacc	aaggacaaat	aacattgaat	tacactattg	tactggagct	tatcggattt	480
cacctgtaga	tgtaaatagt	agaccttcct	cctgccttac	taatttttctt	ctaaatggtc	540
gttctgtttt	attggaacaa	ccacgaaagt	caggttctaa	agtcattagt	catatgctta	600
gtagccatgg	aggagagatt	tttttgacag	tccttagcag	ttctcgatcc	attctagaag	660
atccaccttc	aattagtga	ggatgtggag	gaagagttac	agactaccgg	attacagatt	720
ttggtgaatt	tatgagggga	aaacagatta	actccttttc	tacaccccg	atataaaatc	780
gatggaagtc	ttgaggtccc	tttggaaccg	agccaaaaga	tcagttaaaa	aaacataccc	840
gttactggcc	tatgatttca	aaaaccacc	attttttaaca	tgcaagcggg	agttccgtta	900
acca						904

<210> 88
 <211> 387
 <212> DNA
 <213> Homo sapien

<400> 88
 cgtctctccc ccagtttgcc gttcacccgg agcgctcggg acttgccgat agtgggtgacg 60
 gcggcaacat gtctgtggct ttgcgggcc cgaggcagcg aggcaagggg gagatcactc 120
 ccgctgcgat tcagaagatg ttggatgaca ataaccatct tattcagtgt ataatggact 180
 ctcagaataa aggaaagacc tcagagtgtt ctcaagtatca gcagatgttg cacacaaact 240
 tgggtatacct tgctacaata gcagattcta atcaaaatat gcagtctctt ttaccagcac 300
 caccacaca gaatatgcct atgggtcctg gagggatgaa tcagagcggg cctccccac 360
 ctccacgctc tcacaacatg ccttcaa 387

<210> 89
 <211> 481
 <212> DNA
 <213> Homo sapien

<400> 89
 tgttcttgga cctgcggtgc tatagagcag gctcttctag gttggcagtt gccatggaat 60
 ctggacccaa aatggttgcc cccgtttgcc tgggtggaaa taacaatgag cagctattgg 120
 tgaaccagca agctatacag attcttgaaa agattttctca gccagtgggtg gtgggtggcca 180
 ttgtaggact gtaccgtaca gggaaatcct acttgatgaa ccatctggca ggacagaatc 240
 atggcttccc tctgggctcc acggtgcagt ctgaaaccaa gggcatctgg atgtgggtgcg 300
 tgccccaccc atccaagcca aaccacaccc tggtccttct ggacaccgaa ggtctgggcg 360
 atgtggaaaa ggggtgaccct aagaatgact cctggatctt tgccctggct gtgctcctgt 420
 gcagcacctt tgtctacaac agcatgagca ccatcaacca ccaggccctg gagcagctgc 480
 a 481

<210> 90
 <211> 491
 <212> DNA
 <213> Homo sapien

<400> 90
 tgaaaactgt tcttggacct gcggtgctat agagcagggt ggcagttgcc atggaatctg 60
 gacccaaaat gttggccccc gtttgcctgg tggaaaataa caatgagcag ctattgggtga 120
 accagcaagc tatacagatt cttgaaaaga tttctcagcc agtgggtgggtg gtggccattg 180
 taggactgta ccgtacaggg aaatcctact tgatgaacca tctggcagga cagaatcatg 240
 gcttccctct gggctccacg gtgcagctctg aaaccaaggg catctggatg tgggtgcgtgc 300
 cccacccatc caagccaaac cacaccctgg tcttcttgga caccgaaggt ctgggcatg 360
 tggaaaaggg tgaccctaag aatgactcct ggatctttgc cctggctgtg ctctgtgca 420
 gcacctttgt ctacaacagc atgagcacca tcaaccacca agccctggag cagctgcatt 480
 atgtgacgga c 491

<210> 91
 <211> 488
 <212> DNA
 <213> Homo sapien

<400> 91
 ttcgacagtc agccgcatct tcttttgcgt cgccagccga gccacatcgc tcagacacca 60
 tggggaaggt gaaggtcgga gtcaacggat ttggtcgtat tgggcgcctg gtcaccaggg 120

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ctgcttttaa ctctggtaaa gtggatattg ttgccatcaa tgaccccttc attgacctca 180
actacatggg ttacatgttc caatatgatt ccacccatgg caaattccat ggcaccgtcg 240
aggctgagaa cgggaagctt gtcacatg gaaatcccat caccatcttc caggagcgag 300
atccctccaa aatcaagtgg ggcgatgctg gcgctgagta cgtcgtggag tccactggcg 360
tcttcaccac catggagaag gctggggctc atttgcaggg gggagccaaa agggatcatca 420
tctctgcccc tctgctgatg ccccatgttc gtcatgggtg tgaacctatga gaagtatgac 480
acagcctc

```

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<210> 92
<211> 384
<212> DNA
<213> Homo sapien

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<400> 92
gacagtcagc cgcattcttct tttgcgtcgc cagccgagcc acatcgtctca gacaccatgg 60
ggaaggtgaa ggtcggagtc aacggatttg gtcgtattgg gcgcctggtc accagggctg 120
cttttaactc tggtaaagtg gatattgttg ccatcaatga ccccttcatt gacctcaact 180
acatggttta catgttccaa tatgattcca cccatggcaa attccatggc accgtcgagg 240
ctgagaacgg gaagcttgtc atcaatggaa atcccatcac catcttccag gagcgagatc 300
cctccaaaat caagtggggc gatactggcg ctgagtacgt cgtggagtcc actggcgtct 360
tcaccaccat ggagaaggct gggg
384

```

```

<210> 93
<211> 162
<212> PRT
<213> Homo sapien

```

```

<400> 93
Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg
1      5      10      15
Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr
20      25      30
Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
35      40      45
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
50      55      60
Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
65      70      75      80
Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
85      90      95
Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu
100     105     110
Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp Pro Glu Arg Asp Met
115     120     125
Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp
130     135     140
Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
145     150     155     160
Val Leu

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<210> 94
<211> 100
<212> PRT

```

<213> Homo sapien

<400> 94

Asp	Leu	Glu	Glu	Ala	Thr	Leu	Gln	His	Glu	Ala	Thr	Ala	Ala	Thr	Leu
1				5					10					15	
Arg	Lys	Lys	His	Ala	Asp	Ser	Val	Ala	Glu	Leu	Gly	Glu	Gln	Ile	Asp
			20					25					30		
Asn	Leu	Gln	Arg	Val	Lys	Gln	Lys	Leu	Glu	Lys	Glu	Lys	Ser	Glu	Met
		35				40						45			
Lys	Met	Glu	Ile	Asp	Asp	Leu	Ala	Cys	Asn	Met	Glu	Val	Ile	Ser	Lys
	50					55					60				
Ser	Lys	Gly	Asn	Leu	Glu	Lys	Met	Cys	Arg	Thr	Leu	Glu	Asp	Gln	Val
65					70					75					80
Ser	Glu	Leu	Lys	Thr	Gln	Glu	Glu	Glu	Gln	Gln	Arg	Leu	Ile	Asn	Glu
				85					90					95	
Leu	Thr	Ala	Gln												
			100												

<210> 95

<211> 99

<212> PRT

<213> Homo sapien

<400> 95

Lys	Ile	Leu	Pro	Leu	Asn	Gly	Asn	Leu	Gln	Ala	Val	Glu	Leu	Gly	Glu
1				5					10					15	
Lys	Arg	Thr	Ser	Ser	Leu	Arg	Ile	Lys	Met	Phe	Arg	Ala	Thr	Arg	Val
			20					25					30		
Thr	Ser	Thr	Ser	Arg	Phe	Leu	Asn	Pro	Tyr	Val	Val	Cys	Phe	Leu	Val
		35				40						45			
Leu	Pro	Gly	Val	Val	Ile	Leu	Ala	Val	Pro	Ile	Ala	Leu	Leu	Val	Tyr
	50					55					60				
Phe	Leu	Ala	Phe	Asp	Gln	Lys	Ser	Tyr	Phe	Tyr	Trp	Ser	Asn	Phe	Pro
65					70					75					80
Leu	Pro	Asn	Val	Glu	Tyr	Asn	Ser	Pro	Phe	Asn	Ser	Pro	Ala	Ser	Pro
				85					90					95	
Gly	Ile	Pro													

<210> 96

<211> 257

<212> PRT

<213> Homo sapien

<400> 96

Val	Gln	Glu	Thr	Ile	His	Glu	His	Asn	Lys	Leu	Ala	Ala	Asn	Ser	Asp
1				5					10					15	
His	Leu	Met	Gln	Ile	Gln	Lys	Cys	Glu	Leu	Val	Leu	Ile	His	Thr	Tyr
			20					25					30		
Pro	Val	Gly	Glu	Asp	Ser	Leu	Val	Ser	Asp	Arg	Ser	Lys	Lys	Glu	Leu
		35				40						45			
Ser	Pro	Val	Leu	Thr	Ser	Glu	Val	His	Ser	Val	Arg	Ala	Gly	Arg	His
	50					55					60				
Leu	Ala	Thr	Lys	Leu	Asn	Ile	Leu	Val	Gln	Gln	His	Phe	Asp	Leu	Ala

```

<210> 97
<211> 128
<212> PRT
<213> Homo sapien

<400> 97
Ser Leu Pro Gln Phe Ala Val His Pro Glu Arg Ser Gly Leu Ala Asp
 1          5          10          15
Ser Gly Asp Gly Gly Asn Met Ser Val Ala Phe Ala Ala Pro Arg Gln
          20          25          30
Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp
          35          40          45
Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
          50          55          60
Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu
65          70          75          80
Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu
          85          90          95
Leu Pro Ala Pro Pro Thr Gln Asn Met Pro Met Gly Pro Gly Gly Met
          100          105          110
Asn Gln Ser Gly Pro Pro Pro Pro Pro Arg Ser His Asn Met Pro Ser
          115          120          125

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<210> 98
<211> 159
<212> PRT
<213> Homo sapien
```

```

<210> 99
<211> 147
<212> PRT
<213> Homo sapien

<400> 99
Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu Asn
 1          5          10          15
Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
          20          25          30
Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
          35          40          45
Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
          50          55          60
Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
65          70          75          80
Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu
          85          90          95
Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
          100          105          110
Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
          115          120          125
Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
          130          135          140
Val Thr Asp
145

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```
<210> 100
<211> 124
<212> PRT
<213> Homo sapien
```

```
<210> 101
<211> 127
<212> PRT
<213> Homo sapien
```

```
<210> 102
<211> 1225
<212> DNA
<213> Homo sapien
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<400> 102						
atggcgggcgc	ggtcgtcgtc	gggggtggcg	gcggcagagg	gggcggcggc	cctggcgggca	60
gcggagacgg	cagccgtgac	ggtggcagcg	gcggcgcggg	acctgggcct	gggggaatga	120
ggcggcccg	gcgggccagc	ggcggagcgg	tgtagcggag	aagctcccc	tcctgtcttc	180
ccttggccga	gccggggggc	cgcgcgcacg	cggccgtcca	gagcgggctc	cccacccctc	240
gactcctgcg	accgcgaccg	caccccccacc	cgggcccgga	ggatgatgaa	gctcaagtcg	300
aaccagaccc	gcacctacga	cggcgacggc	tacaagaagc	gggccgcgatg	cctgtgtttc	360
cgcagcgaga	gcgaggagga	ggtgctactc	gtgagcagta	gtcgccatcc	agacagatgg	420

attgtccctg	gaggaggcat	ggagcccgag	gaggagccaa	gtgtggcagc	agttcgtgaa	480
gtctgtgagg	aggctggagt	aaaagggaca	ttgggaagat	tagttggaat	ttttgagaac	540
caggagagga	agcacaggac	gtatgtctat	gtgctcattg	tcactgaagt	gctggaagac	600
tggaagatt	cagttaacat	tggaaggaag	agggaatggt	ttaaaataga	agacgccata	660
aaagtgtctg	agtatcacia	acccgtgcag	gcatcatatt	ttgaaacatt	gaggcaaggc	720
tactcagcca	acaatggcac	cccagtcgtg	gccaccacat	actcggtttc	tgctcagagc	780
tcgatgtcag	gcatcagatg	actgaagact	tcctgtaaga	gaaatggaaa	ttggaaacta	840
gactgaagtg	caaattcttc	ctctcaccct	ggctctttcc	acttctcaca	ggcctcctct	900
ttcaaataag	gcatggtggg	cagcaaagaa	agggtgtatt	gataatgttg	ctgtttggtg	960
ttaagtgatg	gggctttttc	ttctgttttt	attgagggtg	ggggttgggt	gtgtaatttg	1020
taagtacttt	tgtgcatgat	ctgtccctcc	ctcttcccac	ccctgcagtc	ctctgaagag	1080
aggccaacag	ccttcccctg	ccttggattc	tgaagtgttc	ctgtttgtct	tatcctggcc	1140
ctggccagac	gttttctttg	atttttaatt	tttttttttt	attaaaagat	accagtatga	1200
gaaaaaaaaa	aaaaaaaaaac	tcgag				1225

<210> 103

<211> 741

<212> DNA

<213> Homo sapien

<400> 103

agaaacctca	atcggattca	gcaaaggaat	ggtgttatta	tcactacata	ccaaatgtta	60
atcaataact	ggcagcaact	ttcaagcttt	aggggcccaag	agtttgtgtg	ggactatgtc	120
atcctcgatg	aagcacataa	aataaaaacc	tcactacta	agtcagcaat	atgtgctcgt	180
gctattcctg	caagtaatcg	cctcctcctc	acaggaaccc	caatccagaa	taattttaca	240
gaactatggg	ccctatttga	ttttgcttgt	caaggggtccc	tgctgggaac	attaaaaact	300
tttaagatgg	agtatgaaaa	tcctattact	agagcaagag	agaaggatgc	taccccagga	360
gaaaaagcct	tggaatttaa	aatatctgaa	aacttaatgg	caatcataaa	accctatttt	420
ctcaggagga	ctaaagaaga	cgtacagaag	aaaaagtcaa	gcaaccacga	ggccagactt	480
aatgaaaaga	atccagatgt	tgatgccatt	tgtgaaatgc	cttccctttc	caggagaaat	540
gattttaatta	tttgatacag	acttgtgcct	ttacaagaag	aaatatacag	gaaatttgtg	600
tcttttagatc	atatcaagga	gttgctaatt	gagacgcgct	cacctttggc	tgagctaggt	660
gtcttaaaaga	agctgtgtga	tcctcctagg	ctgctgtctg	cacgggcttg	ttgtttgcta	720
aatcttgga	cattctctgc	t				741

<210> 104

<211> 321

<212> DNA

<213> Homo sapien

<400> 104

ttgctctgcg	tcataaaaga	caccaaactg	ctgtgctata	aaagttccaa	ggaccagcag	60
cctcagatgg	aactgccact	ccaaggctgt	aacattacgt	acatcccga	agacagcaaa	120
aagaagaagc	acgagctgaa	gattactcag	cagggcacgg	acccgcttgt	tctcgccgtc	180
cagagcaagg	aacaggccga	gcagtggctg	aaggatgatca	aagaagccta	cagtggttgt	240
agtggccccg	tggattcaga	gtgtcctcct	ccaccaagct	ccccggtgca	caaggcagaa	300
ctggagaaga	aactgtcttc	a				321

<210> 105

<211> 389

<212> DNA

<213> Homo sapien

<400> 105

cagcactggc	cacactataa	aattcagggt	cagaaaaaca	gggtaagtca	cagacagcaa	60
cgcttccagc	atattatctt	tttgcaccca	tgggcaattt	gagaaaattt	accttttagaa	120
cgaactctgt	taaagggtaca	gacagtacaa	tactttttat	tcagaagggt	tctgcataaa	180
ggatgatagtc	ttttgactta	atatattatt	gtctcctgcc	ttgtgtttct	ggaatgaatg	240
aagggtcatta	tttagaagat	aatctgggtt	gtattttgtgt	cgtcagattg	aattttcatt	300
gcacatgcta	cttaatgtct	ttaccaaata	ataacaaagg	gaaagaaaac	caaatataga	360
tgtataataa	ggaaaagctg	gcctataga				389

<210> 106

<211> 446

<212> DNA

<213> Homo sapien

<400> 106

gccacatttg	ccctgggtcat	agtttaaaca	ccagggtcctg	tgtcacatct	ttttgggtgcc	60
acaagtatca	ctccattggt	cagagagtaa	tgtattagtt	ctgcccatt	cattcttcac	120
ttttatttct	tccatttcat	tagcatttat	atcagctcaa	gaagttaagg	ttagaaaatt	180
ttccacttca	aatttttcagt	acagaaatgt	gctgtgatgt	ttgacaagac	tatttcataag	240
taagtgaagt	aatgttttatt	ggcctctgct	ctcctctgtg	tcagacctag	gaagcctgag	300
gattacttag	ttgttctgtc	tctgggtcca	caggcagaat	ttggcccatc	caaagactgg	360
ccaagtgcc	aaaaaaggcc	tgattaggcc	ctgaaattca	gtgaaattct	gcctgaagaa	420
acctcttatt	gaatttgaaa	accata				446

<210> 107

<211> 467

<212> DNA

<213> Homo sapien

<400> 107

ccgccgctgc	cgctgccttc	ctgggattgg	agtctcgagc	tttcttcggt	cgttcgccgg	60
cgggttcgcg	cccttctcgc	gcctcggggc	tgcgaggctg	gggaaggggt	tggagggggc	120
tggtgatcgc	cgcgtttaag	ttgcgctcgg	ggcggccatg	tcggccggcg	aggctcgagcg	180
cctagtgtcg	gagctgagcg	gcgggaccgg	aggggatgag	gaggaagagt	ggctctatgg	240
cgatgaagat	gaagttgaaa	ggccagaaga	agaaaatgcc	agtgcataatc	ctccatctgg	300
aattgaagat	gaaactgctg	aaaatgggtg	acaaaaaccg	aaagtgactg	agaccgaaga	360
tgatagtgat	agtgcagcgc	atgatgatga	agatgatgtg	catgtcacta	taggagacat	420
taaaacggga	gcaccacagt	atgggaggtta	tggtagagca	cctgtaa		467

<210> 108

<211> 491

<212> DNA

<213> Homo sapien

<400> 108

gaaagataca	acttccccaa	cccaaaccgg	tttgtggagg	acgacatgga	taagaatgaa	60
atcgctctctg	ttgcgtaccg	ttaccgcagg	tggaaagcttg	gagatgatat	tgaccttatt	120
gtccgttgtg	agcacgatgg	cgatcatgact	ggagccaacg	gggaagtgtc	cttcatcaac	180
atcaagacac	tcaatgagtg	ggattccagg	cactgtaatg	gcgttgactg	gcgtcagaag	240
ctggactctc	agcgaggggc	tgtcattgcc	acggagctga	agaacaacag	ctacaagttg	300
gcccggtgga	cctgctgtgc	tttgctggct	ggatctgagt	acctcaagct	tggttatgtg	360
tctcggtacc	acgtgaaaga	ctcctcacgc	cacgtcatcc	taggcacca	gcagttcaag	420
cctaattgagt	ttgccagcca	gatcaacctg	agcgtggaga	atgcctgagg	cattttacgc	480
tgcgtcattg	a					491

<210> 109
 <211> 489
 <212> DNA
 <213> Homo sapien

<400> 109
 ctcagatagt actgaaccct ttatcaacta tgtttttttca gtctgacaac caaggcggct 60
 actaagtgac taaggggcag gtagtatata gtgtggataa gcaggacaaa ggggtgattc 120
 acatcccagg caggacagag caggagatca tgagatttca tcactcagga tggcttgtga 180
 tttattttat tttattcttt tttttttttg agatggagtc tcactcttgc ccaggctgga 240
 gtgcagtggg gcgatcttgg ctcaactgcaa cctctgcctc ctgggttcaa gcagttctcc 300
 tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt 360
 tgtactttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac 420
 ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca 480
 tgccccgggc 489

<210> 110
 <211> 391
 <212> DNA
 <213> Homo sapien

<400> 110
 gcggagtcgg ctggctgacc cgagcgtctg tctccgccgg gaaccctggg gcatggagag 60
 gtctgagtac ctcgcccgcg gcgcacgctg catcgcgagg ccaggctgcc gctgtcccag 120
 tggagttcca ggagcaccac ctgagtgagg tgcagaatat ggcatctgag gagaagctgg 180
 agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc 240
 cgatggagta taagggggag ctagcctcct atgatatgcg gctgaggcgt aagttggact 300
 tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc 360
 tagacctggt gatcattcga gagcagacag a 391

<210> 111
 <211> 172
 <212> PRT
 <213> Homo sapien

<400> 111
 Met Met Lys Leu Lys Ser Asn Gln Thr Arg Thr Tyr Asp Gly Asp Gly
 1 5 10 15
 Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
 20 25 30
 Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
 35 40 45
 Pro Gly Gly Gly Met Glu Pro Glu Glu Glu Pro Ser Val Ala Ala Val
 50 55 60
 Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
 65 70 75 80
 Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
 85 90 95
 Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn
 100 105 110
 Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
 115 120 125
 Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg
 130 135 140

Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
 145 150 155 160
 Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
 165 170

<210> 112
 <211> 247
 <212> PRT
 <213> Homo sapien

<400> 112
 Arg Asn Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr
 1 5 10 15
 Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly
 20 25 30
 Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile
 35 40 45
 Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala
 50 55 60
 Ser Asn Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln
 65 70 75 80
 Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly
 85 90 95
 Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala
 100 105 110
 Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile
 115 120 125
 Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr
 130 135 140
 Lys Glu Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu
 145 150 155 160
 Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu
 165 170 175
 Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln
 180 185 190
 Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu
 195 200 205
 Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys
 210 215 220
 Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu
 225 230 235 240
 Asn Leu Gly Thr Phe Ser Ala
 245

<210> 113
 <211> 107
 <212> PRT
 <213> Homo sapien

<400> 113
 Leu Leu Cys Val Ile Lys Asp Thr Lys Leu Leu Cys Tyr Lys Ser Ser
 1 5 10 15
 Lys Asp Gln Gln Pro Gln Met Glu Leu Pro Leu Gln Gly Cys Asn Ile
 20 25 30

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<210> 114
<211> 155
<212> PRT
<213> Homo sapien
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<210> 115
<211> 129
<212> PRT
<213> Homo sapien
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<400> 115															
Gly	Val	Arg	Trp	Leu	Thr	Arg	Ala	Leu	Val	Ser	Ala	Gly	Asn	Pro	Gly
1				5					10					15	
Ala	Trp	Arg	Gly	Leu	Ser	Thr	Ser	Ala	Ala	Ala	His	Ala	Ala	Ser	Arg
			20					25						30	
Ser	Gln	Ala	Ala	Ala	Val	Pro	Val	Glu	Phe	Gln	Glu	His	His	Leu	Ser
		35					40					45			
Glu	Val	Gln	Asn	Met	Ala	Ser	Glu	Glu	Lys	Leu	Glu	Gln	Val	Leu	Ser
	50					55					60				
Ser	Met	Lys	Glu	Asn	Lys	Val	Ala	Ile	Ile	Gly	Lys	Ile	His	Thr	Pro
65					70					75					80

Met	Glu	Tyr	Lys	Gly	Glu	Leu	Ala	Ser	Tyr	Asp	Met	Arg	Leu	Arg	Arg
				85					90					95	
Lys	Leu	Asp	Leu	Phe	Ala	Asn	Val	Ile	His	Val	Lys	Ser	Leu	Pro	Gly
			100					105					110		
Tyr	Met	Thr	Arg	His	Asn	Asn	Leu	Asp	Leu	Val	Ile	Ile	Arg	Glu	Gln
		115					120					125			

Thr

<210> 116
 <211> 550
 <212> DNA
 <213> Homo sapien

<400> 116

gaattcggca	ccagcctcag	agccccccag	cccggctacc	acccccctgcg	gaaagggtacc	60
catctgcatt	cctgcccgtc	gggacctggt	ggacagtcca	gcctccttgg	cctctagcct	120
tggctcaccg	ctgcctagag	ccaaggagct	catcctgaat	gaccttcccg	ccagcactcc	180
tgcttccaaa	tcctgtgact	cctccccgcc	ccaggacgct	tccacccccca	ggcccagctc	240
ggccagtcac	ctctgccagc	ttgctgccaa	gccagcacct	tccacggaca	gcgtcgccct	300
gaggagcccc	ctgactctgt	ccagtccctt	caccacgtcc	ttcagcctgg	gctcccacag	360
cactctcaac	ggagacctct	ccgtgcccag	ctcctacgtc	agcctccacc	tgtcccccca	420
ggtcagcagc	tctgtggtgt	acggacgctc	ccccgtgatg	gcatttgagt	ctcatcccca	480
tctccgaggg	tcatecgtct	cttcctccct	accagcatc	cctgggggaa	agccggccta	540
ctccttccac						550

<210> 117
 <211> 154
 <212> DNA
 <213> Homo sapien

<400> 117

ttctgaggga	aagccgagtg	gagtggggcga	cccggcggcg	gtgacaatga	gttttcttgg	60
aggctttttt	ggtcccattt	gtgagattga	tggtgccctt	aatgatgggg	aaaccaggaa	120
aatggcagaa	atgaaaactg	aggatggcaa	agta			154

<210> 118
 <211> 449
 <212> DNA
 <213> Homo sapien

<400> 118

gaattcggca	ccaggggccc	cagccccgagt	gtcgccgcga	tggcttcgcc	gcagctctgc	60
cgcgcgctgg	tgtcggcgca	atgggtggcg	gaggcgctgc	gggccccgcg	cgctgggcag	120
cctctgcagc	tgctggacgc	ctcctggtac	ctgccgaagc	tggggcgcgca	cgcgcgacgc	180
gagttcgagg	agcgccacat	cccgggcgcc	gctttcttcg	acatcgacca	gtgcagcgac	240
cgcacctcgc	cctacgacca	catgctgccc	ggggccgagc	atttcgcgga	gtacgcaggc	300
cgcctggggc	tgggcgcggc	cacccacgtc	gtgatctacg	acgccagcga	ccagggcctc	360
tactccgcc	cgcgcgtctg	gtggatgttc	cgcgccttcg	gccaccacgc	cgtgtcactg	420
cttgatggcg	gcctccgcca	ctggctgcg				449

<210> 119
 <211> 642
 <212> DNA

<213> Homo sapien

<400> 119

gaattcggca	cgagcagtaa	cccgaccgcc	gctggtcttc	gctggacacc	atgaatcaca	60
ctgtccaaac	cttcttctct	cctgtcaaca	gtggccagcc	ccccaactat	gagatgctca	120
aggaggagca	cgaggtggct	gtgctggggg	cgccccacaa	ccctgctccc	ccgacgtcca	180
ccgtgatcca	catccgcagc	gagacctccg	tgcccgacca	tgtcgtctgg	tccctgttca	240
acaccctctt	catgaacccc	tgtgccttgg	gcttcatagc	attcgcctac	tccgtgaagt	300
ctagggacag	gaagatgggt	ggcgacgtga	ccggggccca	ggcctatgcc	tccaccgcca	360
agtgcctgaa	catctggggc	ctgattcttg	gcacctcat	gaccattctg	ctcatcgtca	420
tcccagtgct	gatcttccag	gcctatggat	agatcaggag	gcatactga	ggccaggagc	480
tctgcccatt	acctgtatcc	cacgtactcc	aacttccatt	cctcgccttg	cccccgagc	540
cgagtcctgt	atcagccctt	tatcctcaca	cgcttttcta	caatggcatt	caataaagtg	600
cacgtgtttc	tggtgaaaaa	aaaaaaaaaa	aaaaaactcg	ag		642

<210> 120

<211> 603

<212> DNA

<213> Homo sapien

<400> 120

gaattcggca	cgagccacaa	cagccactac	gactgcatcc	actggatcca	cggccacccc	60
gtcctccacc	ccgggaacag	ctccccctcc	caaagtgctg	accagcccgg	ccaccacacc	120
catgtccacc	atgtccacaa	tccacacctc	ctctactcca	gagaccaccc	acacctccac	180
agtgtgacc	accacagcca	ccatgacaag	ggccaccaat	tccacggcca	cacctcctc	240
cactctgggg	acgaccggga	tcctcactga	gctgaccaca	acagccacta	caactgcagc	300
cactggatcc	acggccaccc	tgctctccac	cccagggacc	acctggatcc	tcacagagcc	360
gagcactata	gccaccgtga	tggtgcccac	cggttccacg	gccaccgcct	cctccactct	420
gggaacagct	cacaccccac	aagtgggtgac	caccatggcc	actatgccc	cagccactgc	480
ctccacgggt	cccagctcgt	ccaccgtggg	gaccacccgc	accctgcag	tgctccccag	540
cagcctgcc	accttcagcg	tgtccactgt	gtcctcctca	gtcctcacca	ccctgagacc	600
cac						603

<210> 121

<211> 178

<212> PRT

<213> Homo sapien

<400> 121

Ser	Glu	Pro	Pro	Ser	Pro	Ala	Thr	Thr	Pro	Cys	Gly	Lys	Val	Pro	Ile
1				5					10					15	
Cys	Ile	Pro	Ala	Arg	Arg	Asp	Leu	Val	Asp	Ser	Pro	Ala	Ser	Leu	Ala
			20					25					30		
Ser	Ser	Leu	Gly	Ser	Pro	Leu	Pro	Arg	Ala	Lys	Glu	Leu	Ile	Leu	Asn
		35				40					45				
Asp	Leu	Pro	Ala	Ser	Thr	Pro	Ala	Ser	Lys	Ser	Cys	Asp	Ser	Ser	Pro
	50					55					60				
Pro	Gln	Asp	Ala	Ser	Thr	Pro	Arg	Pro	Ser	Ser	Ala	Ser	His	Leu	Cys
65					70				75					80	
Gln	Leu	Ala	Ala	Lys	Pro	Ala	Pro	Ser	Thr	Asp	Ser	Val	Ala	Leu	Arg
			85					90						95	
Ser	Pro	Leu	Thr	Leu	Ser	Ser	Pro	Phe	Thr	Thr	Ser	Phe	Ser	Leu	Gly
			100					105						110	
Ser	His	Ser	Thr	Leu	Asn	Gly	Asp	Leu	Ser	Val	Pro	Ser	Ser	Tyr	Val

		115				120					125						
Ser	Leu	His	Leu	Ser	Pro	Gln	Val	Ser	Ser	Ser	Val	Val	Tyr	Gly	Arg		
	130					135					140						
Ser	Pro	Val	Met	Ala	Phe	Glu	Ser	His	Pro	His	Leu	Arg	Gly	Ser	Ser		
145					150					155					160		
Val	Ser	Ser	Ser	Leu	Pro	Ser	Ile	Pro	Gly	Gly	Lys	Pro	Ala	Tyr	Ser		
				165					170					175			

Phe His

<210> 122
 <211> 36
 <212> PRT
 <213> Homo sapien

<400> 122

Met	Ser	Phe	Leu	Gly	Gly	Phe	Phe	Gly	Pro	Ile	Cys	Glu	Ile	Asp	Val		
1				5					10					15			
Ala	Leu	Asn	Asp	Gly	Glu	Thr	Arg	Lys	Met	Ala	Glu	Met	Lys	Thr	Glu		
			20					25					30				
Asp	Gly	Lys	Val														
			35														

<210> 123
 <211> 136
 <212> PRT
 <213> Homo sapien

<400> 123

Met	Ala	Ser	Pro	Gln	Leu	Cys	Arg	Ala	Leu	Val	Ser	Ala	Gln	Trp	Val		
1				5					10					15			
Ala	Glu	Ala	Leu	Arg	Ala	Pro	Arg	Ala	Gly	Gln	Pro	Leu	Gln	Leu	Leu		
			20					25					30				
Asp	Ala	Ser	Trp	Tyr	Leu	Pro	Lys	Leu	Gly	Arg	Asp	Ala	Arg	Arg	Glu		
		35					40					45					
Phe	Glu	Glu	Arg	His	Ile	Pro	Gly	Ala	Ala	Phe	Phe	Asp	Ile	Asp	Gln		
	50				55					60							
Cys	Ser	Asp	Arg	Thr	Ser	Pro	Tyr	Asp	His	Met	Leu	Pro	Gly	Ala	Glu		
65					70				75						80		
His	Phe	Ala	Glu	Tyr	Ala	Gly	Arg	Leu	Gly	Val	Gly	Ala	Ala	Thr	His		
			85					90						95			
Val	Val	Ile	Tyr	Asp	Ala	Ser	Asp	Gln	Gly	Leu	Tyr	Ser	Ala	Pro	Arg		
			100					105					110				
Val	Trp	Trp	Met	Phe	Arg	Ala	Phe	Gly	His	His	Ala	Val	Ser	Leu	Leu		
		115					120					125					
Asp	Gly	Gly	Leu	Arg	His	Trp	Leu										
	130					135											

<210> 124
 <211> 133
 <212> PRT
 <213> Homo sapien

<400> 124

[illegible]

$\langle 210 \rangle$	126
$\langle 211 \rangle$	509

<212> DNA

<213> Homo sapien

<400> 126

gaattcggca	cgagccaagt	accccctgag	gaatctgcag	cctgcacatctg	agtacaccgt	60
atccctcgtg	gccataaagg	gcaaccaaga	gagccccc	gccactggag	tctttaccac	120
actgcagcct	gggagctcta	ttccacctta	caacaccgag	gtgactgaga	ccaccattgt	180
gatcacatgg	acgcctgctc	caagaattgg	ttttaagctg	gggtgtacgac	caagccaggg	240
aggagaggca	ccacgagaag	tgacttcaga	ctcaggaagc	atcgttgtgt	ccggcttgac	300
tccaggagta	gaatacgtct	acaccatcca	agtcctgaga	gatggacagg	aaagagatgc	360
gccaattgta	aacaaagtgg	tgacaccatt	gtctccacca	acaaacttgc	atctggaggg	420
aaaccctgac	actggagtgc	tcacagtctc	ctggagagga	gcaccacccc	agacattact	480
gggtatagaa	ttaccacaac	ccctacaaa				509

<210> 127

<211> 500

<212> DNA

<213> Homo sapien

<400> 127

gaattcggca	cgagccactg	atgtccgggg	agtcagccag	gagcttgggg	aaggggaagcg	60
cgcccccg	gccggtccc	gagggctcga	tccgcaccta	cagcatgagg	ttctgcccgt	120
ttgctgagag	gacgcgtcta	gtcctgaagg	ccaaggggaat	caggcatgaa	gtcatcaata	180
tcaacctgaa	aaataagcct	gagtgggttct	ttaagaaaaa	tccctttggt	ctgggtgccag	240
ttctggaaaa	cagtcagggg	cagctgatct	acgagtctgc	catcacctgt	gagtacctgg	300
atgaagcata	cccaggggaag	aagctgttgc	cggatgaccc	ctatgagaaa	gcttgccaga	360
agatgatctt	agagttgttt	tctaaggtgc	catccttggt	aggaagcttt	attagaagcc	420
aaaataaaga	agactatgct	ggcctaaaag	aagaatttcg	taaagaattt	accaagctag	480
aggagggttct	gactaataag					500

<210> 128

<211> 500

<212> DNA

<213> Homo sapien

<400> 128

agctttcctc	tgctgccgct	cggtcacgct	tgtgcccga	ggaggaaaca	gtgacagacc	60
tggagactgc	agttctctat	ccttcacaca	gctctttcac	catgcctgga	tcacttcctt	120
tgaatgcaga	agcttgctgg	ccaaaagatg	tgggaattgt	tgcccttgag	atctattttc	180
cttctcaata	tgttgatcaa	gcagagttgg	aaaaatatga	tgggtgtagat	gctggaaagt	240
ataccattgg	cttggggccag	gccaaagatg	gcttctgcac	agatagagaa	gatattaact	300
ctctttgcat	gactgtgggt	cagaatctta	tggagagaaa	taacctttcc	tatgattgca	360
ttgggcggct	ggaagttgga	acagagacaa	tcacgacaa	atcaaagtct	gtgaagacta	420
atttgatgca	gctgtttgaa	gagtctggga	atacagatat	agaaggaatc	gacacaacta	480
atgcatgcta	tggaggcaca					500

<210> 129

<211> 497

<212> DNA

<213> Homo sapien

<400> 129

gaattcggca	cgagcagagg	tctccagagc	cttctctctc	ctgtgcaaaa	tggcaactct	60
taaggaaaaa	ctcattgcac	cagttgcgga	agaagaggca	acagttccaa	acaataagat	120

cactgtagtg	ggtgttggac	aagttggtat	ggcgtgtgct	atcagcattc	tgggaaagtc	180
tctggctgat	gaacttgctc	ttgtggatgt	tttggaagat	aagcttaaag	gagaaatgat	240
ggatctgcag	catgggagct	tatttcttca	gacacctaaa	attgtggcag	ataaagatta	300
ttctgtgacc	gccaatctta	agattgtagt	ggtaactgca	ggagtcctgc	agcaagaagg	360
ggagagtcgg	ctcaatctgg	tgcagagaaa	tgttaatgtc	ttcaaattca	ttattcctca	420
gatcgtcaag	tacagtcctg	attgcatcat	aattgtgggt	tccaacccag	tggacattct	480
tacgtatggt	acctgga					497

<210> 130

<211> 383

<212> DNA

<213> Homo sapien

<400> 130

gaattcggca	cgagggccgc	ggctgccgac	tgggtcccct	gccgctgtcg	ccaccatggc	60
tccgcaccgc	cccgcgcccg	cgctgctttg	cgcgctgtcc	ctggcgctgt	gcgcgctgtc	120
gctgcccgtc	cgcgcggcca	ctgcgtcgcg	gggggcgtcc	caggcggggg	cgccccaggg	180
gcgggtgccc	gaggcgcggc	ccaacagcat	ggtggtggaa	caccccgagt	tcctcaaggc	240
aggggaaggag	cctggcctgc	agatctggcg	tgtggagaaa	gttcgatctg	gtggcccgtg	300
cccaccaacc	tttatggaga	cttcttcacg	ggcgacgcct	acgtcatcct	gaagacagtg	360
cagcttaaga	acggaaaatc	ttg				383

<210> 131

<211> 509

<212> DNA

<213> Homo sapien

<400> 131

gaattcggca	cgagagtcag	ccgcatcttc	ttttgcgtcg	ccagccgagc	cacatcgctc	60
agacaccatg	gggaagggtga	aggtcggagt	caacggattt	ggtcgtattg	ggcgccctgg	120
caccaggggt	gcttttaact	ctggtaaagt	ggatattggt	gccatcaatg	accccttcat	180
tgacctcaac	tacatgggtt	acatgttcca	atatgattcc	acccatggca	aattccatgg	240
caccgtcaag	gctgagaacg	ggaagcttgt	catcaatgga	aatcccatca	ccatcttcca	300
ggagcgagat	ccctccaaaa	tcaagtgggg	cgatgctggc	gctgagtacg	tcgtggagtc	360
cactggccgt	cttcaccacc	atggagaagg	ctggggctca	tttgagggg	ggagccaaaa	420
gggtcatcat	ctctgcccc	tctgctgacg	cccccatggt	cgtcatgggt	gtgaaccatg	480
agaagtatga	caacagcctc	aagatcatc				509

<210> 132

<211> 357

<212> DNA

<213> Homo sapien

<400> 132

gaattcggca	cgagtaagaa	gaagccccta	gaccacagct	ccacaccatg	gactggacct	60
ggaggatcct	cttcttgggt	gcagcagcaa	caggtgccca	ctcccagggt	caactggtgc	120
aatctgggtc	tgagttgaag	aagcctgggg	cctcagtga	ggtttcctgc	aaggcttctg	180
gacacatctt	cagtatctat	ggtttgaatt	gggtgcgaca	ggcccctgg	caaggccttg	240
agtggatggg	atggatcaaa	gtcgacactg	cgaacccaac	gtatgccag	ggcttcacag	300
gacgatttgt	cttctccctg	gacacctctg	tcagcacggc	atatctgcag	atcagca	357

<210> 133

<211> 468

<212> DNA

<213> Homo sapien

<400> 133

gaattcggca	cgaggcgccc	cgaaccgtcc	tcttgctgct	ctcggcgggc	ctggccctga	60
ccgagacctg	ggccggctcc	cactccatga	ggtatttcga	caccgccatg	tcccggcccg	120
gccgcgggga	gccccgcttc	atctcagtgg	gctacgtgga	cgacacgcag	ttcgtgaggt	180
tcgacagcga	cgccgcgagt	ccgagagagg	agccgcgggc	gccgtggata	gagcaggagg	240
ggccggagta	ttgggaccgg	aacacacaga	tcttcaagac	caacacacag	actgaccgag	300
agagcctgcg	gaacctgcgc	ggctactaca	accagagcga	ggccgggtct	cacaccctcc	360
agagcatgta	cggctgcgac	gtggggccgg	acgggcgcct	cctccgcggg	cataaccagt	420
acgcctacga	cggcaaggat	tacatcgccc	tgaacgagga	cctgcgct		468

<210> 134

<211> 214

<212> DNA

<213> Homo sapien

<400> 134

gaattcggca	cgagctgcgt	cctgctgagc	tctgtttctt	ccagcacctc	ccaacccact	60
agtgcctggg	tctcttgctc	caccaggaac	aagccaccat	gtctcgccag	tcaagtgtgt	120
ccttccggag	cgggggcagt	cgtagcttca	gcaccgcctc	tgccatcacc	ccgtctgtct	180
cccgcaccag	cttcacctcc	gtgtcccggg	ccgg			214

<210> 135

<211> 355

<212> DNA

<213> Homo sapien

<400> 135

gaattcggca	cgaggtgaac	aggaccgctc	gccatggggc	gtgtgatecc	tggacagagg	60
aagggcgccg	ggtctgtgtt	ccgcgcgcac	gtgaagcacc	gtaaaggcgc	tgcgcgcctg	120
cgcgccgtgg	atttcgctga	gcggcacggc	tacatcaagg	gcacgcgtaa	ggacatcatc	180
cacgaccccg	gccgcggcgc	gcccctcgcc	aagggtggtc	tccgggatcc	gtatcggttt	240
aagaagcggg	cggagctggt	cattgccgcc	gagggcattc	acacggggcc	gtttgtgtat	300
tgcggcaaga	aggcccagct	caacattggc	aatgtgctcc	ctgtgggcac	catgc	355

<210> 136

<211> 242

<212> DNA

<213> Homo sapien

<400> 136

gaattcggca	cgagccagct	cctaaccgcg	agtgateccg	cagcctccgc	ctcccagagg	60
gcccggattg	cagacggagt	ctccttcaact	cagtgcctca	tggtgcccag	gctggagtg	120
agtgggtgtg	tctcggctcg	ctacaacatc	cacctcccag	cagcctgcct	tggcctccca	180
aagtgccgag	attgcagctc	tctgcccggc	cgccaccctc	gtctgggaag	tgaggatgct	240
gt						242

<210> 137

<211> 424

<212> DNA

<213> Homo sapien

<400> 137

gaattcggca	cgagcccaga	tcccagaggtc	cgacagcgcc	cggcccagat	ccccacgcct	60
gccaggagca	agccgagagc	cagccgggccc	gcgcactccg	actccgagca	gtctctgtcc	120
ttcgacccga	gccccgcgcc	ctttccggga	cccctgcccc	gcgggcagcg	ctgccaacct	180
gccggccatg	gagaccccgt	cccagcggcg	cgccacccgc	agcggggcgc	aggccagctc	240
cactccgctg	tcgcccaccc	gcataccccc	gctgcaggag	aaggaggacc	tgcaggagct	300
caatgatcgc	ttggcggtct	acatcgaccg	tgtgcgctcg	ctggaaacgg	agaacgcagg	360
gctgcgcctt	cgcatacccg	agtctgaaga	ggtggtcagc	cgcgaggtgt	ccggcatcaa	420
ggcc						424

<210> 138

<211> 448

<212> DNA

<213> Homo sapien

<400> 138

gaattcggca	cgagcctgtg	ttccaggagc	cgaatcagaa	atgtcctcct	caggcacgcc	60
agacttacct	gtcctactca	ccgatttgaa	gattcaatat	actaagatct	tcataaacia	120
tgaatggcat	gattcagtg	gtggcaagaa	atttcctgtc	tttaatcctg	caactgagga	180
ggagctctgc	caggtagaag	aaggagataa	ggaggatgtt	gacaaggcag	tgaaggccgc	240
aagacaggct	tttcagattg	gatccccgtg	gcgtactatg	gatgcttccg	agagggggcg	300
actattatac	aagttggctg	atttaatcga	aagagatcgt	ctgctgctgg	ccgacaatgg	360
agtcaatgaa	tgggtgaaaa	ctctattcca	atgcatactc	gaatgattta	gcaggctgca	420
tcaaaacatt	gcgctactgt	gcagggttg				448

<210> 139

<211> 510

<212> DNA

<213> Homo sapien

<400> 139

gaattcggca	cgagggttccg	tgcagctcac	ggagaagcga	atggacaaag	tcggcaagta	60
ccccaaaggag	ctgcgcaagt	gctgcgagga	cggcatgcgg	gagaacccca	tgaggttctc	120
gtgccagcgc	cggacccggt	tcctctccct	ggcgaggcgt	gcaagaagg	cttcctggac	180
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<210> 140

<211> 360

<212> DNA

<213> Homo sapien

<400> 140

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cgatgttttg	ggggtcaaac	ccaatgctac	tcaggaagaa	ttgaaaaagg	cttataggaa	180
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ttctcaagct	tacgaagttc	tctctgatgc	aaagaaaagg	gaattatatg	acaaaggagg	300
agaacaggca	attaaagagg	gtggagcagg	tggcggtttt	ggctccccca	tggacatctt	360

<210> 141

<211> 483
 <212> DNA
 <213> Homo sapien

<400> 141

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tcttcgtgaa	gaccctgact	ggtaagacca	tcaccctcga	ggtggagccc	agtgcacca	420
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tga						483

<210> 142
 <211> 500
 <212> DNA
 <213> Homo sapien

<400> 142

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<210> 143
 <211> 400
 <212> DNA
 <213> Homo sapien

<400> 143

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gcctgaagga	cccatggaca	cgtgactcca	gtgtttctca	caacatctta	gatcaagttg	360
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<210> 144
 <211> 243
 <212> DNA
 <213> Homo sapien

<400> 144

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<210> 145
<211> 450
<212> DNA
<213> Homo sapien
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<210> 146
<211> 451
<212> DNA
<213> Homo sapien
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<210> 147
<211> 400
<212> DNA
<213> Homo sapien
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<210> 148
<211> 503
<212> DNA
<213> Homo sapien
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<400> 148
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<210> 149

<211> 1061

<212> DNA

<213> Homo sapien

<400> 149

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<210> 150

<211> 781

<212> DNA

<213> Homo sapien

<400> 150

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<210> 151
 <211> 3275
 <212> DNA
 <213> Homo sapien

<400> 151

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<210> 152

<211> 2179

<212> DNA

<213> Homo sapien

<400> 152

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<210> 153

<211> 2109
 <212> DNA
 <213> Homo sapien

<400> 153

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<210> 154
 <211> 1411
 <212> DNA
 <213> Homo sapien

<400> 154

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<210> 155

<211> 678

<212> DNA

<213> Homo sapien

<400> 155

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<210> 156

<211> 2668

<212> DNA

<213> Homo sapien

<400> 156

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<210> 157

<211> 2313

<212> DNA

<213> Homo sapien

<400> 157

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<210> 158

<211> 2114

<212> DNA

<213> Homo sapien

<400> 158

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<210> 159

<211> 278

<212> DNA

<213> Homo sapien

<400> 159

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tgcagaatga	gaatcactcc	taaaataggt	aatggtaaaa	attaaattga	caattacctc	180
tctctatgca	gaaggaaata	tcacctatat	gacatcatca	tcattctattg	atacttgctg	240
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<210> 160

<211> 848

<212> DNA

<213> Homo sapien

<400> 160

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<210> 161

<211> 432

<212> DNA

<213> Homo sapien

<400> 161

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cctcctgtcc	cagcgagagc	aggaaatagt	ggtcctgcag	cagcaactgc	aggaagccag	360
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<210> 162

<211> 433

<212> DNA

<213> Homo sapien

<400> 162

gattcggcac	gagccggagc	tgggttgctc	ctgctcccgt	ctccaagtcc	tggtagctcc	60
ttcaagctgg	gagagggctc	tagtccctgg	ttctgaacac	tctgggggtc	tcgggtgcag	120
gccgccatga	gcaaacggaa	ggcgccgcag	gagactctca	acgggggaat	caccgacatg	180
ctcacagaac	tcgcaaactt	tgagaagaac	gtgagccaag	ctatccacaa	gtacaatgct	240
tacagaaaag	cagcatctgt	tatagcaaaa	taccacacac	aaataaagag	tggagctgaa	300
gctaagaaat	tgcctggagt	aggaacaaaa	attgctgaaa	agattgatga	gttttttagca	360
actggaaaat	tacgtaaact	ggaaaagatt	cggcaggatg	atacgagttc	atccatcaat	420
ttcctgactc	gag					433

<210> 163

<211> 432

<212> DNA

<213> Homo sapien

<400> 163

gaattcggca	ccagatgagg	ccaacgaggt	gacggacagc	gcgtacatgg	gctccgagag	60
cacctacagt	gagtgtgaga	ccttcacgga	cgaggacacc	agcaccctgg	tgcaccctga	120
gctgcaacct	gaaggggacg	cagacagtgc	cggcggtctg	gccgtgccct	ctgagtgcct	180
ggacgccatg	gaggagcccg	accatggtgc	cctgctgctg	ctcccaggca	ggcctcacc	240
ccatggccag	tctgtcatca	cgggtgatcg	gggcgaggag	cactttgagg	actacggtga	300
aggcagtgag	gcggagctgt	ccccagagac	cctatgcaac	gggcagctgg	gctgcagtga	360
ccccgctttc	ctcacgcccc	gtccgacaaa	gcggtctctc	agcaagaagg	tggcaaggta	420
cctgcaccag	tc					432

<210> 164

<211> 395

<212> DNA

<213> Homo sapien

<400> 164

gacacttgaa	tcatgggtga	cgttaaaaaat	tttctgtatg	cctggtgtgg	caaaaggaag	60
atgaccccat	cctatgaaat	tagagcagtg	gggaacaaaa	acaggcagaa	attcatgtgt	120
gaggttcagg	tggaagggtta	taattacact	ggcatgggaa	attccaccaa	taaaaaagat	180
gcacaaagca	atgctgccag	agactttgtt	aactattttg	ttcgaataaa	tgaaataaag	240
agtgaagaag	ttccagcttt	tggggtagca	tctccgcccc	cacttactga	tactcctgac	300
actacagcaa	atgctgaagg	catcttggtg	acatcgaata	tgactttgat	aataaatacc	360

ggttcctgaa aaaaaaaaaa aaaaaaaaaac tcgag

395

<210> 165
 <211> 503
 <212> DNA
 <213> Homo sapien

<400> 165

gaattcggca	ccaggaacgc	tcggtgagag	gcgaggagc	ggtaactacc	ccggttgccg	60
acagctcggc	gctccttccc	gctccctcac	acaccggcct	cagcccgcac	cggcagtaga	120
agatggtgaa	agaaacaact	tactacgatg	ttttgggggt	caaacccaat	gctactcagg	180
aagaattgaa	aaaggcttat	aggaaactgg	ccttgaagta	ccatcctgat	aagaacccaa	240
atgaaggaga	gaagttttaa	cagatttctc	aagcttacga	agttctctct	gatgcaaaga	300
aaagggaatt	atatgacaaa	ggaggagAAC	aggcaattaa	agaggggtga	gcagggtggc	360
gttttggctc	ccccatggac	atctttgata	tgttttttgg	aggaggagga	aggatgcaga	420
gagaaaggag	aggtaaaaat	gttgtacatc	agctctcagt	aaccctagaa	gacttatata	480
atggtgcaac	aagaaaactg	gct				503

<210> 166
 <211> 893
 <212> DNA
 <213> Homo sapien

<400> 166

gaattcggca	cgagaggaac	ttctcttgac	gagaagagag	accaaggagg	ccaagcaggg	60
gctgggccag	agggtgccaac	atggggaaac	tgaggctcgg	ctcggaaggg	tgagagttag	120
actacatctc	aaaaaaaaaa	aaaaaaaaaa	aaaagaaaga	aaagaaaaga	aaaaagaaag	180
aacggaagta	gttgtaggta	gtggtatggt	ggtatgagtc	tgttttctgt	tacttataac	240
aacaacaaca	acaaaaaacg	ctgaaactgg	gtaatttata	aagaaaagga	aaaaaagcag	300
aaaaaaatca	ggaagaagag	aaaggaaaag	aagacaaata	aatgaaattt	atgtattaca	360
gttctgaagg	ctgagacatc	ccagggtcaag	ggtccacact	tggcgagggc	tttcttgctg	420
gtggagactc	tttgtggagt	cctgggacag	tgcagaagga	tcacgcctcc	ctaccgctcc	480
aagcccagcc	ctcagccatg	gcattgcccc	tggtatcaggc	cattggcctc	ctcgtggcca	540
tcttccacaa	gtactccggc	agggaggggt	acaagcacac	cctgagcaag	aaggagctga	600
aggagctgat	ccagaaggag	ctcaccattg	gctcgaagct	gcaggatgct	gaaattgcaa	660
ggctgatgga	agacttggac	cggaacaagg	accaggaggt	gaacttccag	gagtatgtca	720
ccttcctggg	ggccttgggt	ttgatctaca	atgaagccct	caagggtctga	aaataaatag	780
ggaagatgga	gacaccctct	gggggtcctc	tctgagtcaa	atccagtggg	gggtaattgt	840
acaataaatt	tttttttggtc	aaatttataa	aaaaaaaaaa	aaaaaaactc	gag	893

<210> 167
 <211> 549
 <212> DNA
 <213> Homo sapien

<400> 167

gaattcggca	cgagcccaga	tcccagaggtc	cgacagcgcc	cgcccagat	ccccacgcct	60
gccaggagca	agccgagagc	cagccggccg	gcgcactccg	actccgagca	gtctctgtcc	120
ttcgaccoga	gccccgcgcc	ctttccggga	cccctgcccc	gcgggcagcg	ctgccaacct	180
gccggccatg	gagaccccgt	cccagcggcg	cgccaccgcg	agcggggcgc	aggccagctc	240
cactccgctg	tcgcccaccc	gcattcaccg	gctgcaggag	aaggaggacc	tgaggagct	300
caatgatcgc	ttggcggtct	acatcgaccg	tgtgcgctcg	ctggaaacgg	agaacgcagg	360
gctgcgcctt	cgcattcaccg	agtctgaaga	ggtggtcagc	cgcgaggtgt	ccggcatcaa	420
ggccgcctac	gaggccgagc	tcgggggatgc	ccgcaagacc	cttgactcag	tagccaagga	480

gcgcgcccgc ctgcagctgg agctgagcaa agtgcgtaga gagtttaagg agctgaaagc 540
gcgcaatac 549

<210> 168
<211> 547
<212> DNA
<213> Homo sapien

<400> 168
gaattcggca cgagatggcg gcaggggtcg aagcggcggc ggaggtggcg gcgacggaga 60
tcaaaatgga ggaagagagc ggcgcgcccg gcgtgccgag cggcaacggg gctccggggc 120
ctaaggggtga aggagaacga cctgctcaga atgagaagag gaaggagaaa aacataaaaa 180
gaggaggcaa tcgctttgag ccatatgcca atccaactaa aagatacaga gccttcatta 240
caaacatacc ttttgatgtg aaatggcagt cacttaaaga cctgggttaa gaaaaagttg 300
gtgaggtaac atacgtggag ctcttaatgg acgctgaagg aaagtcaagg ggatgtgctg 360
ttgttgaatt caagatggaa gagagcatga aaaaagctgc ggaagtccta aacaagcata 420
gtctgagcgg aagaccactg aaagtcaaag aagatcctga tggatgaacat gccaggagag 480
caatgcaaaa ggctggaaga cttggaagca cagtatttgt agcaaactctg gattataaag 540
ttggctg 547

<210> 169
<211> 547
<212> DNA
<213> Homo sapien

<400> 169
gaattcggca ccaggagtcc gactgtgctc gctgctcagc gccgcacccg gaagatgagg 60
ctcgccgtgg gagccctgct ggtctgcgcc gtcctggggc tgtgtctggc tgtccctgat 120
aaaactgtga gatgggtgtgc agtgctcgag catgaggcca ctaagtgcc gagtttccgc 180
gaccatatga aaagcgtcat tccatccgat ggtcccagtg ttgcttgtgt gaagaaagcc 240
tcctaccttg attgcatcag ggccattgag gcaaacgaag cggatgctgt gacactggat 300
gcaggtttgg tgtatgatgc ttacctggct cccaataacc tgaagcctgt ggtggcagag 360
ttctatgggt caaaagagga tccacagact ttctattatg ctgttgctgt ggtgaagaag 420
gatagtggct tccagatgaa ccagcttcga ggcaagaagt cctgccacac gggcttaggc 480
aggctccgctg ggtggaacat ccccataggc ttactttact gtgacttacc tgagccacgt 540
aaacctc 547

<210> 170
<211> 838
<212> DNA
<213> Homo sapien

<400> 170
gaattcggca ccagaggagc tcggcctgag ctgcgccacg atgtccgggg agtcagccag 60
gagcttgggg aagggaagcg cgcgcccggg gccggtcccg gagggctcga tccgcatcta 120
cagcatgagg ttctgcccgt ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat 180
caggcatgaa gtcatacaata tcaacctgaa aaataagcct gagtggttct ttaagaaaaa 240
tcccttttgg ctggtgccag ttctggaaaa cagtcagggt cagctgatct acgagtctgc 300
catcacctgt gagtacctgg atgaagcata cccagggaag aagctgttgc cggatgacct 360
ctatgagaaa gcttgccaga agatgatctt agagttgttt tctaagggtc catccttggg 420
aggaagcttt attagaagcc aaaataaaga agactatgat ggcctaaaag aagaatttcg 480
taaagaattt accaagctag aggaggttct gactaataag aagacgacct tctttgggtg 540
caattctatc tctatgattg attacctcat ctggccctgg tttgaacggc tggaagcaat 600
gaagttaaata gagtgtgtag accacactcc aaaactgaaa ctgtggatgg cagccatgaa 660

ggaagatccc	acagtctcag	ccctgcttac	tagtgagaaa	gactggcaag	gtttcctaga	720
gctctactta	cagaacagcc	ctgaggcctg	tgactatggg	ctctgaaggg	ggcaggagtc	780
agcaataaag	ctatgtctga	tatttttcctt	cactaaaaaa	aaaaaaaaaa	aactcgag	838

<210> 171

<211> 547

<212> DNA

<213> Homo sapien

<400> 171

gaattcggca	ccagcgggat	ttgggtcgca	gttcttgttt	gtggattgct	gtgatcgta	60
cttgacaatg	cagatcttcg	tgaagactct	gactggtaag	accatcaccc	tcgaggttga	120
gcccagtgac	accatcgaga	atgtcaaggc	aaagatccaa	gataaggaag	gcacccctcc	180
tgaccagcag	aggctgatct	ttgctggaaa	acagctggaa	gatgggcgca	ccctgtctga	240
ctacaacatc	cagaaagagt	ccaccctgca	cctgggtgctc	cgtctcagag	gtgggatgca	300
aatcttcgtg	aagacactca	ctggcaagac	catcacccctt	gaggtcgagc	ccagtgcacac	360
catcgagaac	gtcaaagcaa	agatccagga	caaggaaggc	attcctcctg	accagcagag	420
gttgatcttt	gccggaaagc	agctggaaga	tgggcgcacc	ctgtctgact	acaacatcca	480
gaaagagtct	accctgcacc	tgggtgctccg	tctcagagggt	gggatgcaga	tcttcgtgaa	540
gaccctg						547

<210> 172

<211> 608

<212> DNA

<213> Homo sapien

<400> 172

gaattcggca	ccagagactt	ctccctctga	ggcctgcgca	ccccctctca	tcagcctgtc	60
caccctcatc	tacaatgggtg	ccctgccatg	tcagtgcac	cctcaagggtt	cactgagttc	120
tgagtgcac	cctcatgggtg	gtcagtgcct	gtgcaagcct	ggagtgggtg	ggcgccgctg	180
tgacctctgt	gccccctggct	actatggctt	tggccccaca	ggctgtcaag	gcgcttgctt	240
gggctgccgt	gatcacacag	ggggtgagca	ctgtgaaagg	tgcattgctg	gtttccacgg	300
ggacccacgg	ctgccatatg	ggggccagtg	ccggccctgt	ccctgtcctg	aaggccctgg	360
gagccaacgg	cactttgcta	cttcttgcca	ccaggatgaa	tattcccagc	agattgtgtg	420
ccactgccgg	gcaggctata	cggggctgcg	atgtgaagct	tgtgcccctg	ggcactttgg	480
ggacccatca	aggccaggtg	gccggtgcca	actgtgtgag	tgcagtggga	acattgaccc	540
aatggatcct	gatgcctgtg	acccccacac	ggggcaatgc	ctgcgctgtt	tacaccacac	600
agagggtc						608

<210> 173

<211> 543

<212> DNA

<213> Homo sapien

<400> 173

gaattcggca	ccagagatca	tccgccagca	gggtctggcc	tcctacgact	acgtgcgccc	60
ccgcctcacg	gctgaggacc	tggttcgaggc	tcggatcatc	tctctcgaga	cctacaacct	120
gctccgggag	ggcaccagga	gcctccgtga	ggctctcgag	gcggagtccg	cctgggtgcta	180
cctctatggc	acgggctccg	tggttggtgt	ctacctgccc	ggttccaggc	agacactgag	240
catctaccag	gctctcaaga	aagggtgct	gagtgccgag	gtggcccgcc	tgctgctgga	300
ggcacaggca	gccacaggct	tcctgctgga	cccgggtgaag	ggggaacggc	tgactgtgga	360
tgaagctgtg	cggaaggggc	tcgtggggcc	cgaactgcac	gaccgcctgc	tctcggtga	420
gcgggcggtc	accggtacc	gtgaccctca	caccgagcag	accatctcgc	tcttccaggc	480
catgaagaag	gaactgatcc	ctactgagga	ggccctgcgg	ctgtggatgc	ccagctggcc	540

acc

543

<210> 174
 <211> 548
 <212> DNA
 <213> Homo sapien

<400> 174

gaattcggca	cgagaaatgg	cggcaggggt	cgaagcggcg	gcggaggtgg	cggcgacgga	60
gatcaaaatg	gaggaagaga	gcggcgcgcc	cggcgtgccg	agcggcaacg	gggctccggg	120
ccctaagggg	gaaggagaac	gacctgctca	gaatgagaag	aggaaggaga	aaaacataaa	180
aagaggaggc	aatcgctttg	agccatatgc	caatccaact	aaaagataca	gagccttcat	240
tacaaacata	ccttttgatg	tgaaatggca	gtcacttaaa	gacctgggta	aagaaaaagt	300
tggtgaggta	acatacgtgg	agctcttaat	ggacgctgaa	ggaaagtcaa	ggggatgtgc	360
tgttggtgaa	ttcaagatgg	aagagagcat	gaaaaaagct	gcggaagtcc	taaacaagca	420
tagtctgagc	ggaagaccac	tgaaagtcaa	agaagatcct	gatggatgaac	atgccaggag	480
agcaatgcaa	aaggtgatgg	ctacgactgg	tgggatgggt	atgggaccag	gtggcccagg	540
aatgatta						548

<210> 175
 <211> 604
 <212> DNA
 <213> Homo sapien

<400> 175

gaattcggca	ccagaggacc	tccaggacat	gttcatcgtc	cataccatcg	aggagattga	60
gggcctgatc	tcagcccatg	accagttcaa	gtccaccctg	ccggacgccg	atagggagcg	120
cgaggccatc	ctggccatcc	acaaggaggc	ccagaggatc	gctgagagca	accacatcaa	180
gctgtcgggc	agcaaccctt	acaccaccgt	caccccgcaa	atcatcaact	ccaagtggga	240
gaaggtgcag	cagctgggtgc	caaaacggga	ccatgccctc	ctggaggagc	agagcaagca	300
gcagtccaac	gagcacctgc	gccgccagtt	cgccagccag	gccaatgttg	tggggccctg	360
gatccagacc	aagatggagg	agatcggggc	catctccatt	gagatgaacg	ggaccctgga	420
ggaccagctg	agccacctga	agcagtatga	acgcagcatc	gtggactaca	agcccaacct	480
ggacctgctg	gagcagcagc	accagcttat	ccaggaggcc	ctcatcttcg	acaacaagca	540
caccaactat	accatggagc	acatccgcgt	gggctgggag	cagctgctca	ccaccattgc	600
ccgg						604

<210> 176
 <211> 486
 <212> DNA
 <213> Homo sapien

<400> 176

gaattcggca	ccagccaagc	tcactattga	atccacgccg	ttcaatgtcg	cagaggggaa	60
ggaggttctt	ctactcgccc	acaacctgcc	ccagaatcgt	attggttaca	gctggtacaa	120
aggcgaaaga	gtggatggca	acagtcta	tgtaggatat	gtaataggaa	ctcaacaagc	180
taccccaggg	cccgcataca	gtggtcgaga	gacaatatac	cccaatgcat	ccctgctgat	240
ccagaacgtc	acccagaatg	acacaggatt	ctatacccta	caagtcataa	agtcagatct	300
tgtgaatgaa	gaagcaaccg	gacagttcca	tgtatacccg	gagctgcccc	agccctccat	360
ctccagcaac	aactccaacc	ccgtggagga	caaggatgct	gtggccttca	cctgtgaacc	420
tgaggttcag	aacacaacct	acctgtgggtg	ggtaaatggg	cagagcctcc	cggtcagtcc	480
caaggc						486

<210> 177

<211> 387
 <212> DNA
 <213> Homo sapien

<400> 177

gaattcggca	ccagggacag	cagaccagac	agtcacagca	gccttgacaa	aacgttcctg	60
gaactcaagc	tcttctccac	agaggaggac	agagcagaca	gcagagacca	tggagtctcc	120
ctcggcccct	ccccacagat	ggtgcatccc	ctggcagagg	ctcctgctca	cagcctcact	180
tctaaccctt	tggaaccgcg	ccaccactgc	caagctcact	attgaatcca	cgccgttcaa	240
tgtcgcagag	gggaaggagg	tgttcttact	tgtccacaat	ctgccccagc	atcttttttg	300
ctacagctgg	tacaaagggt	aaagagtggg	tggcaaccgt	caaattatag	gatatgtaat	360
aggaactcaa	caagctaccc	caggggcc				387

<210> 178
 <211> 440
 <212> DNA
 <213> Homo sapien

<400> 178

gaattcggca	cgaggagaag	cagaaaaaca	aggaatttag	ccagacttta	gaaaatgaga	60
aaaatacctt	actgagtcag	atatcaacaa	aggatggtga	actaaaaatg	cttcaggagg	120
aagtaaccaa	aatgaacctg	ttaaatcagc	aaatccaaga	agaactctct	agagttacca	180
aactaaagga	gacagcagaa	gaagagaaag	atgatttgga	agagaggctt	atgaatcaat	240
tagcagaact	taatggaagc	attgggaatt	actgtcagga	tgttacagat	gcccaaataa	300
aaaatgagct	attggaatct	gaaatgaaga	accttaaaaa	gtgtgtgagt	gaattggaag	360
aagaaaagca	gcagttagtc	aaggaaaaaa	ctaagggtgga	atcagaaata	cgaaaggaat	420
atttggaaga	aatacaaggt					440

<210> 179
 <211> 443
 <212> DNA
 <213> Homo sapien

<400> 179

gaattcggca	ccagcggggg	gctacggcgg	cggctacggc	ggcgtcctga	ccgcgtccga	60
cgggctgctg	gcgggcaacg	agaagctaac	catgcagAAC	ctcaacgacc	gcctggcctc	120
ctacctggac	aagggtgcgc	ccctggaggc	ggccaacggc	gagctagagg	tgaagatccg	180
cgactggtac	cagaagcagg	ggcctggggc	ctcccgcgac	tacagccact	actacacgac	240
catccaggac	ctgcgggaca	agattcttgg	tgccaccatt	gagaactcca	ggattgtcct	300
gcagatcgac	aacgcccgtc	tggctgcaga	tgacttccga	accaagtttg	agacggaaca	360
ggctctgcgc	atgagcgtgg	aggccgacat	caacggcctg	cgcagggtgc	tggatgagct	420
gaccctggcc	aggaccgacc	tgg				443

<210> 180
 <211> 403
 <212> DNA
 <213> Homo sapien

<400> 180

gaattcggca	cgaggttatg	agagtcgact	tcaatgttcc	tatgaagaac	aaccagataa	60
caaacaacca	gaggattaag	gctgctgtcc	caagcatcaa	attctgcttg	gacaatggag	120
ccaagtcggt	agtccttatg	agccacctag	gccggcctga	tgggtgtgcc	atgcctgaca	180
agtactcctt	agagccagtt	gctgtagaac	tcagatctct	gctgggcaag	gatgttctgt	240
tcttgaagga	ctgtgtaggc	ccagaagtgg	agaaagcctg	tgccaacca	gctgctgggt	300

ctgtcatcct gctggagaac ctccgctttc atgtggagga agaaggggaag ggaaaagatg 360
 cttctgggaa caaggttaaa gccgagccag ccaaaataga agc 403

<210> 181
 <211> 493
 <212> DNA
 <213> Homo sapien

<400> 181
 gaattcggca ccagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct 60
 taaggaaaaa ctcatcgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
 cactgtagtg ggtgttggaac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
 tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
 ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
 ttctgtgacc gccaatctta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
 ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
 gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
 tacgtatggt acc 493

<210> 182
 <211> 209
 <212> PRT
 <213> Homo sapien

<400> 182
 Ala Phe Ser Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly
 1 5 10 15
 Ala Leu Gln Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro Leu Thr
 20 25 30
 Ala Lys Lys Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg His Phe
 35 40 45
 Pro Tyr Ala Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln Val Leu
 50 55 60
 Arg Thr Leu Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val Arg Val
 65 70 75 80
 Val Thr Leu Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala Glu Glu
 85 90 95
 Glu Ala Glu Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln Gln Tyr
 100 105 110
 Arg Gln Val His Leu Leu Pro Gly Leu Trp Glu Gln Gly Trp Cys Glu
 115 120 125
 Ile Thr Ala His Leu Leu Ala Leu Pro Glu His Asp Ala Arg Glu Lys
 130 135 140
 Val Leu Gln Thr Leu Gly Val Leu Leu Thr Thr Cys Arg Asp Arg Tyr
 145 150 155 160
 Arg Gln Asp Pro Gln Leu Gly Arg Thr Leu Ala Ser Leu Gln Ala Glu
 165 170 175
 Tyr Gln Val Leu Ala Ser Leu Glu Leu Gln Asp Gly Glu Asp Glu Gly
 180 185 190
 Tyr Phe Gln Glu Leu Leu Gly Ser Val Asn Ser Leu Leu Lys Glu Leu
 195 200 205
 Arg

<210> 183
 <211> 255
 <212> PRT
 <213> Homo sapien

<400> 183
 Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Pro
 1 5 10 15
 Lys Met Glu Glu Glu Ser Gly Ala Pro Cys Val Pro Ser Gly Asn Gly
 20 25 30
 Ala Pro Gly Pro Lys Gly Glu Glu Arg Pro Thr Gln Asn Glu Lys Arg
 35 40 45
 Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr Ser
 50 55 60
 Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe Asp
 65 70 75 80
 Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu
 85 90 95
 Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly
 100 105 110
 Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
 115 120 125
 Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys
 130 135 140
 Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
 145 150 155 160
 Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly
 165 170 175
 Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg
 180 185 190
 Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile
 195 200 205
 Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe
 210 215 220
 Asn Gly Gln Leu Leu Phe Asp Arg Pro Met His Val Lys Met Asp Glu
 225 230 235 240
 Arg Ala Leu Pro Lys Gly Asp Phe Phe Pro Pro Glu Arg His Ser
 245 250 255

<210> 184
 <211> 188
 <212> PRT
 <213> Homo sapien

<400> 184
 Leu Ser Gly Ser Cys Ile Arg Arg Glu Gln Thr Pro Glu Lys Glu Lys
 1 5 10 15
 Gln Val Val Leu Phe Glu Glu Ala Ser Trp Thr Cys Thr Pro Ala Cys
 20 25 30
 Gly Asp Glu Pro Arg Thr Val Ile Leu Leu Ser Ser Met Leu Ala Asp
 35 40 45
 His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
 50 55 60
 His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val

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<210> 185
<211> 746
<212> PRT
<213> Homo sapien
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<400> 185															
Asp 1	Lys	His	Leu	Lys 5	Asp	Leu	Leu	Ser	Lys 10	Leu	Leu	Asn	Ser	Gly 15	Tyr
Phe	Glu	Ser	Ile 20	Pro	Val	Pro	Lys	Asn 25	Ala	Lys	Glu	Lys	Glu 30	Val	Pro
Leu	Glu	Glu 35	Glu	Met	Leu	Ile	Gln 40	Ser	Glu	Lys	Lys	Thr 45	Gln	Leu	Ser
Lys	Thr 50	Glu	Ser	Val	Lys	Glu 55	Ser	Glu	Ser	Leu	Met 60	Glu	Phe	Ala	Gln
Pro 65	Glu	Ile	Gln	Pro	Gln 70	Glu	Phe	Leu	Asn	Arg 75	Arg	Tyr	Met	Thr	Glu 80
Val	Asp	Tyr	Ser	Asn 85	Lys	Gln	Gly	Glu	Glu 90	Gln	Pro	Trp	Glu 95	Ala	Asp
Tyr	Ala	Arg	Lys 100	Pro	Asn	Leu	Pro	Lys 105	Arg	Trp	Asp	Met	Leu 110	Thr	Glu
Pro	Asp	Gly 115	Gln	Glu	Lys	Lys	Gln 120	Glu	Ser	Phe	Lys	Ser 125	Trp	Glu	Ala
Ser	Gly 130	Lys	His	Gln	Glu	Val 135	Ser	Lys	Pro	Ala	Val 140	Ser	Leu	Glu	Gln
Arg 145	Lys	Gln	Asp	Thr	Ser 150	Lys	Leu	Arg	Ser	Thr 155	Leu	Pro	Glu	Glu	Gln 160
Lys	Lys	Gln	Glu	Ile 165	Ser	Lys	Ser	Lys	Pro 170	Ser	Pro	Ser	Gln	Trp	Lys 175
Gln	Asp	Thr	Pro 180	Lys	Ser	Lys	Ala	Gly 185	Tyr	Val	Gln	Glu	Glu 190	Gln	Lys
Lys	Gln 195	Glu	Thr	Pro	Lys	Leu	Trp 200	Pro	Val	Gln	Leu	Gln 205	Lys	Glu	Gln
Asp	Pro 210	Lys	Lys	Gln	Thr	Pro 215	Lys	Ser	Trp	Thr	Pro 220	Ser	Met	Gln	Ser
Glu 225	Gln	Asn	Thr	Thr	Lys 230	Ser	Trp	Thr	Thr	Pro 235	Met	Cys	Glu	Glu	Gln 240
Asp	Ser	Lys	Gln	Pro	Glu	Thr	Pro	Lys	Ser 250	Trp	Glu	Asn	Asn	Val	Glu 255

Ser	Gln	Lys	His	Ser	Leu	Thr	Ser	Gln	Ser	Gln	Ile	Ser	Pro	Lys	Ser
			260					265					270		
Trp	Gly	Val	Ala	Thr	Ala	Ser	Leu	Ile	Pro	Asn	Asp	Gln	Leu	Leu	Pro
		275					280					285			
Arg	Lys	Leu	Asn	Thr	Glu	Pro	Lys	Asp	Val	Pro	Lys	Pro	Val	His	Gln
	290					295					300				
Pro	Val	Gly	Ser	Ser	Ser	Thr	Leu	Pro	Lys	Asp	Pro	Val	Leu	Arg	Lys
305					310					315					320
Glu	Lys	Leu	Gln	Asp	Leu	Met	Thr	Gln	Ile	Gln	Gly	Thr	Cys	Asn	Phe
				325					330					335	
Met	Gln	Glu	Ser	Val	Leu	Asp	Phe	Asp	Lys	Pro	Ser	Ser	Ala	Ile	Pro
			340					345					350		
Thr	Ser	Gln	Pro	Pro	Ser	Ala	Thr	Pro	Gly	Ser	Pro	Val	Ala	Ser	Lys
		355						360					365		
Glu	Gln	Asn	Leu	Ser	Ser	Gln	Ser	Asp	Phe	Leu	Gln	Glu	Pro	Leu	Gln
	370					375					380				
Val	Phe	Asn	Val	Asn	Ala	Pro	Leu	Pro	Pro	Arg	Lys	Glu	Gln	Glu	Ile
385					390					395					400
Lys	Glu	Ser	Pro	Tyr	Ser	Pro	Gly	Tyr	Asn	Gln	Ser	Phe	Thr	Thr	Ala
				405					410					415	
Ser	Thr	Gln	Thr	Pro	Pro	Gln	Cys	Gln	Leu	Pro	Ser	Ile	His	Val	Glu
			420					425					430		
Gln	Thr	Val	His	Ser	Gln	Glu	Thr	Ala	Ala	Asn	Tyr	His	Pro	Asp	Gly
		435					440					445			
Thr	Ile	Gln	Val	Ser	Asn	Gly	Ser	Leu	Ala	Phe	Tyr	Pro	Ala	Gln	Thr
	450					455					460				
Asn	Val	Phe	Pro	Arg	Pro	Thr	Gln	Pro	Phe	Val	Asn	Ser	Arg	Gly	Ser
465					470					475					480
Val	Arg	Gly	Cys	Thr	Arg	Gly	Gly	Arg	Leu	Ile	Thr	Asn	Ser	Tyr	Arg
				485					490					495	
Ser	Pro	Gly	Gly	Tyr	Lys	Gly	Phe	Asp	Thr	Tyr	Arg	Gly	Leu	Pro	Ser
			500					505					510		
Ile	Ser	Asn	Gly	Asn	Tyr	Ser	Gln	Leu	Gln	Phe	Gln	Ala	Arg	Glu	Tyr
		515					520					525			
Ser	Gly	Ala	Pro	Tyr	Ser	Gln	Arg	Asp	Asn	Phe	Gln	Gln	Cys	Tyr	Lys
	530					535					540				
Arg	Gly	Gly	Thr	Ser	Gly	Gly	Pro	Arg	Ala	Asn	Ser	Arg	Ala	Gly	Trp
545					550					555					560
Ser	Asp	Ser	Ser	Gln	Val	Ser	Ser	Pro	Glu	Arg	Asp	Asn	Glu	Thr	Phe
				565					570					575	
Asn	Ser	Gly	Asp	Ser	Gly	Gln	Gly	Asp	Ser	Arg	Ser	Met	Thr	Pro	Val
			580					585					590		
Asp	Val	Pro	Val	Thr	Asn	Pro	Ala	Ala	Thr	Ile	Leu	Pro	Val	His	Val
		595					600					605			
Tyr	Pro	Leu	Pro	Gln	Gln	Met									

Val	Leu	Val	Ser	Ala	Tyr	Ala	Asn	Asp	Gly	Ala	Pro	Asp	His	Glu	Thr
	690					695					700				
Ala	Ser	Asn	His	Ala	Ile	Leu	Gln	Leu	Phe	Gln	Gly	Asp	Gln	Ile	Trp
705					710					715					720
Leu	Arg	Leu	His	Arg	Gly	Ala	Ile	Tyr	Gly	Ser	Ser	Trp	Lys	Tyr	Ser
				725					730					735	
Thr	Phe	Ser	Gly	Tyr	Leu	Leu	Tyr	Gln	Asp						
			740					745							

<210> 186

<211> 705

<212> PRT

<213> Homo sapien

<400> 186

Ala	Leu	Leu	Asn	Val	Arg	Gln	Pro	Pro	Ser	Thr	Thr	Thr	Phe	Val	Leu
1				5					10					15	
Asn	Gln	Ile	Asn	His	Leu	Pro	Pro	Leu	Gly	Ser	Thr	Ile	Val	Met	Thr
			20					25					30		
Lys	Thr	Pro	Pro	Val	Thr	Thr	Asn	Arg	Gln	Thr	Ile	Thr	Leu	Thr	Lys
		35					40					45			
Phe	Ile	Gln	Thr	Thr	Ala	Ser	Thr	Arg	Pro	Ser	Val	Ser	Ala	Pro	Thr
	50					55					60				
Val	Arg	Asn	Ala	Met	Thr	Ser	Ala	Pro	Ser	Lys	Asp	Gln	Val	Gln	Leu
65					70					75					80
Lys	Asp	Leu	Leu	Lys	Asn	Asn	Ser	Leu	Asn	Glu	Leu	Met	Lys	Leu	Lys
				85					90				95		
Pro	Pro	Ala	Asn	Ile	Ala	Gln	Pro	Val	Ala	Thr	Ala	Ala	Thr	Asp	Val
			100					105					110		
Ser	Asn	Gly	Thr	Val	Lys	Lys	Glu	Ser	Ser	Asn	Lys	Glu	Gly	Ala	Arg
		115					120					125			
Met	Trp	Ile	Asn	Asp	Met	Lys	Met	Arg	Ser	Phe	Ser	Pro	Thr	Met	Lys
	130					135					140				
Val	Pro	Val	Val	Lys	Glu	Asp	Asp	Glu	Pro	Glu	Glu	Glu	Asp	Glu	Glu
145					150					155					160
Glu	Met	Gly	His	Ala	Glu	Thr	Tyr	Ala	Glu	Tyr	Met	Pro	Ile	Lys	Leu
				165					170					175	
Lys	Ile	Gly	Leu	Arg	His	Pro	Asp	Ala	Val	Val	Glu	Thr	Ser	Ser	Leu
			180					185					190		
Ser	Ser	Val	Thr	Pro	Pro	Asp	Val	Trp	Tyr	Lys	Thr	Ser	Ile	Ser	Glu
		195					200					205			
Glu	Thr	Ile	Asp	Asn	Gly	Trp	Leu	Ser	Ala	Leu	Gln	Leu	Glu	Ala	Ile
	210					215					220				
Thr	Tyr	Ala	Ala	Gln	Gln	His	Glu	Thr	Phe	Leu	Pro	Asn	Gly	Asp	Arg
225					230					235					240
Ala	Gly	Phe	Leu	Ile	Gly	Asp	Gly	Ala	Gly	Val	Gly	Lys	Gly	Arg	Thr
				245					250					255	
Ile	Ala	Gly	Ile	Ile	Tyr	Glu	Asn	Tyr	Leu	Leu	Ser	Arg	Lys	Arg	Ala
			260					265					270		
Leu	Trp	Phe	Ser	Val	Ser	Asn	Asp	Leu	Lys	Tyr	Asp	Ala	Glu	Arg	Asp
		275					280					285			
Leu	Arg	Asp	Ile	Gly	Ala	Lys	Asn	Ile	Leu	Val	His	Ser	Leu	Asn	Lys
	290					295					300				
Phe	Lys	Tyr	Gly	Lys	Ile	Ser	Ser	Lys	His	Asn	Gly	Ser	Val	Lys	Lys

305					310					315					320
Gly	Val	Ile	Phe	Ala	Thr	Tyr	Ser	Ser	Leu	Ile	Gly	Glu	Ser	Gln	Ser
				325					330					335	
Gly	Gly	Lys	Tyr	Lys	Thr	Arg	Leu	Lys	Gln	Leu	Leu	His	Trp	Cys	Gly
			340					345					350		
Asp	Asp	Phe	Asp	Gly	Val	Ile	Val	Phe	Asp	Glu	Cys	His	Lys	Ala	Lys
		355					360					365			
Asn	Leu	Cys	Pro	Val	Gly	Ser	Ser	Lys	Pro	Thr	Lys	Thr	Gly	Leu	Ala
	370					375					380				
Val	Leu	Glu	Leu	Gln	Asn	Lys	Leu	Pro	Lys	Ala	Arg	Val	Val	Tyr	Ala
385				390					395						400
Ser	Ala	Thr	Gly	Ala	Ser	Glu	Pro	Arg	Asn	Met	Ala	Tyr	Met	Asn	Arg
				405					410					415	
Leu	Gly	Ile	Trp	Gly	Glu	Gly	Thr	Pro	Phe	Arg	Glu	Phe	Ser	Asp	Phe
			420				425						430		
Ile	Gln	Ala	Val	Glu	Arg	Arg	Gly	Val	Gly	Ala	Met	Glu	Ile	Val	Ala
	435						440					445			
Met	Asp	Met	Lys	Leu	Arg	Gly	Met	Tyr	Ile	Ala	Arg	Gln	Leu	Ser	Phe
	450					455					460				
Thr	Gly	Val	Thr	Phe	Lys	Ile	Glu	Glu	Val	Leu	Leu	Ser	Gln	Ser	Tyr
465					470					475					480
Val	Lys	Met	Tyr	Asn	Lys	Ala	Val	Lys	Leu	Trp	Val	Ile	Ala	Arg	Glu
				485					490					495	
Arg	Phe	Gln	Gln	Ala	Ala	Asp	Leu	Ile	Asp	Ala	Glu	Gln	Arg	Met	Lys
			500					505					510		
Lys	Ser	Met	Trp	Gly	Gln	Phe	Trp	Ser	Ala	His	Gln	Arg	Phe	Phe	Lys
	515						520					525			
Tyr	Leu	Cys	Ile	Ala	Ser	Lys	Val	Lys	Arg	Val	Val	Gln	Leu	Ala	Arg
	530					535					540				
Glu	Glu	Ile	Lys	Asn	Gly	Lys	Cys	Val	Val	Ile	Gly	Leu	Gln	Ser	Thr
545					550				555						560
Gly	Glu	Ala	Arg	Thr	Leu	Glu	Ala	Leu	Glu	Glu	Gly	Gly	Gly	Glu	Leu
				565					570					575	
Asn	Asp	Phe	Val	Ser	Thr	Ala	Lys	Gly	Val	Leu	Gln	Ser	Leu	Ile	Glu
			580					585					590		
Lys	His	Phe	Pro	Ala	Pro	Asp	Arg	Lys	Lys	Leu	Tyr	Ser	Leu	Leu	Gly
	595					600						605			
Ile	Asp	Leu	Thr	Ala	Pro	Ser	Asn	Asn	Ser	Ser	Pro	Arg	Asp	Ser	Pro
	610					615					620				
Cys	Lys	Glu	Asn	Lys	Ile	Lys	Lys	Arg	Lys	Gly	Glu	Glu	Ile	Thr	Arg
625					630					635					640
Glu	Ala	Lys	Lys	Ala	Arg	Lys	Val	Gly	Gly	Leu	Thr	Gly	Ser	Ser	Ser
				645					650					655	
Asp	Asp	Ser	Gly	Ser	Glu	Ser	Asp	Ala	Ser	Asp	Asn	Glu	Glu	Ser	Asp
			660				665					670			
Tyr	Glu	Ser	Ser	Lys	Asn	Met	Ser	Ser	Gly	Asp	Asp	Asp	Asp	Phe	Asn
	675					680						685			
Pro	Phe	Leu	Asp	Glu	Ser	Asn	Glu	Asp	Asp	Glu	Asn	Asp	Pro	Trp	Leu
	690					695				700					
Ile															
705															

<210> 187

<211> 595

<213> Homo sapien

<400> 187

Glu 1	Ser	Pro	Arg	His 5	Arg	Gly	Glu	Gly	Gly	Gly	Glu	Trp	Gly	Pro	Gly
Val	Pro	Arg	Glu	Arg	Arg	Glu	Ser	Ala	Gly	Glu	Trp	Gly	Ala	Asp	Thr
			20					25					30		
Pro	Lys	Glu	Gly	Gly	Glu	Ser	Ala	Gly	Glu	Trp	Gly	Ala	Glu	Val	Pro
		35					40					45			
Arg	Gly	Arg	Gly	Glu	Gly	Ala	Gly	Glu	Trp	Gly	Pro	Asp	Thr	Pro	Lys
	50					55					60				
Glu	Arg	Gly	Gln	Gly	Val	Arg	Glu	Trp	Gly	Pro	Glu	Ile	Pro	Gln	Glu
65					70					75					80
His	Gly	Glu	Ala	Thr	Arg	Asp	Trp	Ala	Leu	Glu	Ser	Pro	Arg	Ala	Leu
				85				90						95	
Gly	Glu	Asp	Ala	Arg	Glu	Leu	Gly	Ser	Ser	Pro	His	Asp	Arg	Gly	Ala
			100					105					110		
Ser	Pro	Arg	Asp	Leu	Ser	Gly	Glu	Ser	Pro	Cys	Thr	Gln	Arg	Ser	Gly
		115					120					125			
Leu	Leu	Pro	Glu	Arg	Arg	Gly	Asp	Ser	Pro	Trp	Pro	Pro	Trp	Pro	Ser
	130					135					140				
Pro	Gln	Glu	Arg	Asp	Ala	Gly	Thr	Arg	Asp	Arg	Glu	Glu	Ser	Pro	Arg
145					150					155					160
Asp	Trp	Gly	Gly	Ala	Glu	Ser	Pro	Arg	Gly	Trp	Glu	Ala	Gly	Pro	Arg
				165					170					175	
Glu	Trp	Gly	Pro	Ser	Pro	Ser	Gly	His	Gly	Asp	Gly	Pro	Arg	Arg	Arg
			180					185					190		
Pro	Arg	Lys	Arg	Arg	Gly	Arg	Lys	Gly	Arg	Met	Gly	Arg	Gln	His	Glu
		195					200					205			
Ala	Ala	Ala	Thr	Ala	Ala	Thr	Ala	Ala	Thr	Ala	Thr	Gly	Gly	Thr	Ala
	210					215					220				
Glu	Glu	Ala	Gly	Ala	Ser	Ala	Pro	Glu	Ser	Gln	Ala	Gly	Gly	Gly	Pro
225					230					235					240
Arg	Gly	Arg	Ala	Arg	Gly	Pro	Arg	Gln	Gln	Gly	Arg	Arg	Arg	His	Gly
				245					250					255	
Thr	Gln	Arg	Arg	Arg	Gly	Pro	Pro	Gln	Ala	Arg	Glu	Glu	Gly	Pro	Arg
			260					265					270		
Asp	Ala	Thr	Thr	Ile	Leu	Gly	Leu	Gly	Thr	Pro	Ser	Gly	Glu	Gln	Arg
		275					280					285			
Ala	Asp	Gln	Ser	Gln	Ala	Leu	Pro	Ala	Leu	Ala	Gly	Ala	Ala	Ala	Ala
	290					295					300				
His	Ala	His	Ala	Ile	Pro	Gly	Ala	Gly	Pro	Ala	Ala	Ala	Pro	Val	Gly
305					310					315					320
Gly	Arg	Gly	Arg	Arg	Gly	Gly	Trp	Arg	Gly	Gly	Arg	Arg	Gly	Gly	Ser
				325					330					335	
Ala	Gly	Ala	Gly	Gly	Gly	Gly	Arg	Gly	Gly	Arg	Gly	Arg	Gly	Arg	Gly
			340					345					350		
Gly	Gly	Arg	Gly	Gly	Gly	Gly	Ala	Gly	Arg	Gly	Gly	Gly	Ala	Ala	Gly
		355													

Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
 405 410 415
 Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
 420 425 430
 Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
 435 440 445
 Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
 450 455 460
 Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
 465 470 475 480
 Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
 485 490 495
 Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
 500 505 510
 Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
 515 520 525
 Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
 530 535 540
 Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
 545 550 555 560
 Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
 565 570 575
 Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
 580 585 590
 Trp Leu Pro
 595

<210> 188
 <211> 376
 <212> PRT
 <213> Homo sapien

<400> 188
 Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
 1 5 10 15
 Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
 20 25 30
 Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
 35 40 45
 Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
 50 55 60
 Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
 65 70 75 80
 Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
 85 90 95
 Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
 100 105 110
 Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
 115 120 125
 Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
 130 135 140
 Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
 145 150 155 160
 His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His

				165					170					175			
Ile	Ser	Gln	Leu	Glu	Gln	Lys	Val	Arg	Glu	Ser	Glu	Leu	Gln	Val	His		
			180					185					190				
Ser	Ala	Leu	Leu	Gly	Arg	Pro	Ala	Pro	Phe	Gly	Asp	Val	Cys	Leu	Leu		
		195					200					205					
Arg	Leu	Gln	Glu	Leu	Gln	Arg	Glu	Asn	Thr	Phe	Leu	Arg	Ala	Gln	Phe		
	210					215					220						
Ala	Gln	Lys	Thr	Glu	Ala	Leu	Ser	Lys	Glu	Lys	Met	Glu	Leu	Glu	Lys		
225					230					235					240		
Lys	Leu	Ser	Ala	Ser	Glu	Val	Glu	Ile	Gln	Leu	Ile	Arg	Glu	Ser	Leu		
			245					250						255			
Lys	Val	Thr	Leu	Gln	Lys	His	Ser	Glu	Glu	Gly	Lys	Lys	Gln	Glu	Glu		
			260					265					270				
Arg	Val	Lys	Gly	Arg	Asp	Lys	His	Ile	Asn	Asn	Leu	Lys	Lys	Lys	Cys		
	275					280					285						
Gln	Lys	Glu	Ser	Glu	Gln	Asn	Arg	Glu	Lys	Gln	Gln	Arg	Ile	Glu	Thr		
	290					295					300						
Leu	Glu	Arg	Tyr	Leu	Ala	Asp	Leu	Pro	Thr	Leu	Glu	Asp	His	Gln	Lys		
305					310					315					320		
Gln	Thr	Glu	Gln	Leu	Lys	Asp	Ala	Glu	Leu	Lys	Asn	Thr	Glu	Leu	Gln		
			325					330						335			
Glu	Arg	Val	Ala	Glu	Leu	Glu	Thr	Leu	Leu	Glu	Asp	Thr	Gln	Ala	Thr		
			340					345					350				
Cys	Arg	Glu	Lys	Glu	Val	Gln	Leu	Glu	Ser	Leu	Arg	Gln	Arg	Glu	Ala		
	355					360					365						
Asp	Leu	Ser	Ser	Ala	Arg	His	Arg										
	370					375											

<210> 189

<211> 160

<212> PRT

<213> Homo sapien

<400> 189

Met	Leu	Glu	Ala	His	Arg	Arg	Gln	Arg	His	Pro	Phe	Leu	Leu	Leu	Gly		
1				5				10						15			
Thr	Thr	Ala	Asn	Arg	Thr	Gln	Ser	Leu	Asn	Tyr	Gly	Cys	Ile	Val	Glu		
			20				25						30				
Asn	Pro	Gln	Thr	His	Glu	Val	Leu	His	Tyr	Val	Glu	Lys	Pro	Ser	Thr		
		35				40						45					
Phe	Ile	Ser	Asp	Ile	Ile	Asn	Cys	Gly	Ile	Tyr	Leu	Phe	Ser	Pro	Glu		
	50					55					60						
Ala	Leu	Lys	Pro	Leu	Arg	Asp	Val	Phe	Gln	Arg	Asn	Gln	Gln	Asp	Gly		
65					70				75						80		
Gln	Leu	Glu	Asp	Ser	Pro	Gly	Leu	Trp	Pro	Gly	Ala	Gly	Thr	Ile	Arg		
			85				90							95			
Leu	Glu	Gln	Asp	Val	Phe	Ser	Ala	Leu	Ala	Gly	Gln	Gly	Gln	Ile	Tyr		
		100					105						110				
Val	His	Leu	Thr	Asp	Gly	Ile	Trp	Ser	Gln	Ile	Lys	Ser	Ala	Gly	Ser		
		115				120						125					
Ala	Leu	Tyr	Ala	Ser	Arg	Leu	Tyr	Leu	Ser	Arg	Tyr	Gln	Asp	Thr	His		
	130				135					140							
Pro	Glu	Arg	Leu	Ala	Lys	His	Thr	Pro	Gly	Gly	Pro	Trp	Ile	Arg	Gly		
145					150					155					160		

<210> 190
 <211> 146
 <212> PRT
 <213> Homo sapien

<400> 190
 Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
 1 5 10 15
 Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
 20 25 30
 Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
 35 40 45
 Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
 50 55 60
 Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu
 65 70 75 80
 Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
 85 90 95
 Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
 100 105 110
 Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
 115 120 125
 Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
 130 135 140
 Ile Leu
 145

<210> 191
 <211> 704
 <212> PRT
 <213> Homo sapien

<400> 191
 Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu
 1 5 10 15
 Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
 20 25 30
 Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
 35 40 45
 Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
 50 55 60
 Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala
 65 70 75 80
 Leu Arg Ala Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
 85 90 95
 Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu
 100 105 110
 Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
 115 120 125
 Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
 130 135 140
 Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys
 145 150 155 160

Ser	Phe	Ile	Gly	Gln	Asn	Lys	Ser	Phe	Phe	Gly	Pro	Leu	Glu	Leu	Val	
				165					170					175		
Glu	Lys	Leu	Cys	Pro	Glu	Ala	Ser	Asp	Ile	Ala	Thr	Ser	Val	Arg	Asn	
			180					185					190			
Leu	Pro	Glu	Leu	Lys	Thr	Ala	Val	Gly	Arg	Gly	Arg	Ala	Trp	Leu	Tyr	
		195					200					205				
Leu	Ala	Leu	Met	Gln	Lys	Lys	Leu	Ala	Asp	Tyr	Leu	Lys	Val	Leu	Ile	
	210					215					220					
Asp	Asn	Lys	His	Leu	Leu	Ser	Glu	Phe	Tyr	Glu	Pro	Glu	Ala	Leu	Met	
225					230					235					240	
Met	Glu	Glu	Glu	Gly	Met	Val	Ile	Val	Gly	Leu	Leu	Val	Gly	Leu	Asn	
				245					250					255		
Val	Leu	Asp	Ala	Asn	Leu	Cys	Leu	Lys	Gly	Glu	Asp	Leu	Asp	Ser	Gln	
			260					265					270			
Val	Gly	Val	Ile	Asp	Phe	Ser	Leu	Tyr	Leu	Lys	Asp	Val	Gln	Asp	Leu	
	275						280					285				
Asp	Gly	Gly	Lys	Glu	His	Glu	Arg	Ile	Thr	Asp	Val	Leu	Asp	Gln	Lys	
	290					295					300					
Asn	Tyr	Val	Glu	Glu	Leu	Asn	Arg	His	Leu	Ser	Cys	Thr	Val	Gly	Asp	
305					310					315					320	
Leu	Gln	Thr	Lys	Ile	Asp	Gly	Leu	Glu	Lys	Thr	Asn	Ser	Lys	Leu	Gln	
			325						330					335		
Glu	Glu	Leu	Ser	Ala	Ala	Thr	Asp	Arg	Ile	Cys	Ser	Leu	Gln	Glu	Glu	
			340					345					350			
Gln	Gln	Gln	Leu	Arg	Glu	Gln	Asn	Glu	Leu	Ile	Arg	Glu	Arg	Ser	Glu	
		355					360					365				
Lys	Ser	Val	Glu	Ile	Thr	Lys	Gln	Asp	Thr	Lys	Val	Glu	Leu	Glu	Thr	
	370					375					380					
Tyr	Lys	Gln	Thr	Arg	Gln	Gly	Leu	Asp	Glu	Met	Tyr	Ser	Asp	Val	Trp	
385					390					395					400	
Lys	Gln	Leu	Lys	Glu	Glu	Lys	Lys	Val	Arg	Leu	Glu	Leu	Glu	Lys	Glu	
				405					410					415		
Leu	Glu	Leu	Gln	Ile	Gly	Met	Lys	Thr	Glu	Met	Glu	Ile	Ala	Met	Lys	
			420					425					430			
Leu	Leu	Glu	Lys	Asp	Thr	His	Glu	Lys	Gln	Asp	Thr	Leu	Val	Ala	Leu	
		435					440					445				
Arg	Gln	Gln	Leu	Glu	Glu	Val	Lys	Ala	Ile	Asn	Leu	Gln	Met	Phe	His	
	450					455					460					
Lys	Ala	Gln	Asn	Ala	Glu	Ser	Ser	Leu	Gln	Gln	Lys	Asn	Glu	Ala	Ile	
465					470					475					480	
Thr	Ser	Phe	Glu	Gly	Lys	Thr	Asn	Gln	Val	Met	Ser	Ser	Met	Lys	Gln	
				485					490					495		
Met	Glu	Glu	Arg	Leu</												

Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
595 600 605
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
610 615 620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
625 630 635 640
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
645 650 655
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
660 665 670
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
675 680 685
Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
690 695 700

<210> 192

<211> 331

<212> PRT

<213> Homo sapien

<400> 192

Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser
1 5 10 15
Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val
20 25 30
Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu
35 40 45
His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp
50 55 60
Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys
65 70 75 80
Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe
85 90 95
Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp
100 105 110
Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp
115 120 125
Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
130 135 140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
145 150 155 160
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
165 170 175
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
180 185 190
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
195 200 205
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
210 215 220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
225 230 235 240
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
245 250 255
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys

			260					265				270					
Cys	Val	Glu	Val	Leu	Pro	Asp	Arg	Asp	Gly	Lys	Arg	Cys	Met	Phe	Cys		
		275						280				285					
Val	Lys	Thr	Ala	Thr	Arg	Thr	Tyr	Glu	Met	Ser	Ala	Ser	Asp	Thr	Arg		
	290					295					300						
Gln	Arg	Gln	Glu	Trp	Thr	Ala	Ala	Ile	Gln	Met	Ala	Ile	Arg	Leu	Gln		
305					310					315					320		
Ala	Glu	Gly	Lys	Thr	Ser	Leu	His	Lys	Asp	Leu							
				325					330								

<210> 193
 <211> 475
 <212> PRT
 <213> Homo sapien

<400> 193

Lys	Asn	Ser	Pro	Leu	Leu	Ser	Val	Ser	Ser	Gln	Thr	Ile	Thr	Lys	Glu		
1				5					10					15			
Asn	Asn	Arg	Asn	Val	His	Leu	Glu	His	Ser	Glu	Gln	Asn	Pro	Gly	Ser		
			20					25					30				
Ser	Ala	Gly	Asp	Thr	Ser	Ala	Ala	His	Gln	Val	Val	Leu	Gly	Glu	Asn		
		35					40					45					
Leu	Ile	Ala	Thr	Ala	Leu	Cys	Leu	Ser	Gly	Ser	Gly	Ser	Gln	Ser	Asp		
	50					55					60						
Leu	Lys	Asp	Val	Ala	Ser	Thr	Ala	Gly	Glu	Glu	Gly	Asp	Thr	Ser	Leu		
65					70				75						80		
Arg	Glu	Ser	Leu	His	Pro	Val	Thr	Arg	Ser	Leu	Lys	Ala	Gly	Cys	His		
				85					90					95			
Thr	Lys	Gln	Leu	Ala	Ser	Arg	Asn	Cys	Ser	Glu	Glu	Lys	Ser	Pro	Gln		
			100					105					110				
Thr	Ser	Ile	Leu	Lys	Glu	Gly	Asn	Arg	Asp	Thr	Ser	Leu	Asp	Phe	Arg		
		115					120					125					
Pro	Val	Val	Ser	Pro	Ala	Asn	Gly	Val	Glu	Gly	Val	Arg	Val	Asp	Gln		
	130					135						140					
Asp	Asp	Asp	Gln	Asp	Ser	Ser	Ser	Leu	Lys	Leu	Ser	Gln	Asn	Ile	Ala		
145					150					155					160		
Val	Gln	Thr	Asp	Phe	Lys	Thr	Ala	Asp	Ser	Glu	Val	Asn	Thr	Asp	Gln		
				165					170					175			
Asp	Ile	Glu	Lys	Asn	Leu	Asp	Lys	Met	Met	Thr	Glu	Arg	Thr	Leu	Leu		
			180					185					190				
Lys	Glu	Arg	Tyr	Gln	Glu	Val	Leu	Asp	Lys	Gln	Arg	Gln	Val	Glu	Asn		
		195					200					205					
Gln	Leu	Gln	Val	Gln	Leu	Lys	Gln	Leu	Gln	Gln	Arg	Arg	Glu	Glu	Glu		
	210					215					220						
Met	Lys	Asn	His	Gln	Glu	Ile	Leu	Lys	Ala	Ile	Gln	Asp	Val	Thr	Ile		
225					230					235					240		
Lys	Arg	Glu	Glu	Thr	Lys	Lys	Lys	Ile	Glu	Lys	Glu	Lys	Lys	Glu	Phe		
				245					250					255			
Leu	Gln	Lys	Glu	Gln	Asp	Leu	Lys	Ala	Glu	Ile	Glu	Lys	Leu	Cys	Glu		
			260					265					270				
Lys	Gly	Arg	Arg	Glu	Val	Trp	Glu	Met	Glu	Leu	Asp	Arg	Leu	Lys	Asn		
		275					280					285					
Gln	Asp	Gly	Glu	Ile	Asn	Arg	Asn	Ile	Met	Glu	Glu	Thr	Glu	Arg	Ala		
	290					295						300					

Trp Lys Ala Glu Ile Leu Ser Leu Glu Ser Arg Lys Glu Leu Leu Val
 305 310 315 320
 Leu Lys Leu Glu Glu Ala Glu Lys Glu Ala Glu Leu His Leu Thr Tyr
 325 330 335
 Leu Lys Ser Thr Pro Pro Thr Leu Glu Thr Val Arg Ser Lys Gln Glu
 340 345 350
 Trp Glu Thr Arg Leu Asn Gly Val Arg Ile Met Lys Lys Asn Val Arg
 355 360 365
 Asp Gln Phe Asn Ser His Ile Gln Leu Val Arg Asn Gly Ala Lys Leu
 370 375 380
 Ser Ser Leu Pro Gln Ile Pro Thr Pro Thr Leu Pro Pro Pro Pro Ser
 385 390 395 400
 Glu Thr Asp Phe Met Leu Gln Val Phe Gln Pro Ser Pro Ser Leu Ala
 405 410 415
 Pro Arg Met Pro Phe Ser Ile Gly Gln Val Thr Met Pro Met Val Met
 420 425 430
 Pro Ser Ala Asp Pro Arg Ser Leu Ser Phe Pro Ile Leu Asn Pro Ala
 435 440 445
 Leu Ser Gln Pro Ser Gln Pro Ser Ser Pro Leu Pro Gly Ser His Gly
 450 455 460
 Arg Asn Ser Pro Gly Leu Gly Ser Leu Val Ser
 465 470 475

<210> 194

<211> 241

<212> PRT

<213> Homo sapien

<400> 194

Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
 1 5 10 15
 Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
 20 25 30
 Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
 35 40 45
 His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
 50 55 60
 Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
 65 70 75 80
 Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
 85 90 95
 Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
 100 105 110
 Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
 115 120 125
 Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Ala Gly Leu Lys Glu
 130 135 140
 Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
 145 150 155 160
 Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
 165 170 175
 Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
 180 185 190
 Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu

	195		200		205
Asp	Pro Thr Val Ser Ala Leu	Leu Thr Ser Glu Lys	Asp Trp Gln Gly		
	210	215	220		
Phe	Leu Glu Leu Tyr Leu Gln	Asn Ser Pro Glu Ala	Cys Asp Tyr Gly		
225	230	235	240		
Leu					

<210> 195
 <211> 138
 <212> PRT
 <213> Homo sapien

	<400> 195
Gln Thr Lys Ile Leu Glu Glu Asp Leu Glu Gln Ile Lys Leu Ser Leu	
1 5 10 15	
Arg Glu Arg Gly Arg Glu Leu Thr Thr Gln Arg Gln Leu Met Gln Glu	
20 25 30	
Arg Ala Glu Glu Gly Lys Gly Pro Ser Lys Ala Gln Arg Gly Ser Leu	
35 40 45	
Glu His Met Lys Leu Ile Leu Arg Asp Lys Glu Lys Glu Val Glu Cys	
50 55 60	
Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu	
65 70 75 80	
Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu	
85 90 95	
Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln	
100 105 110	
Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln	
115 120 125	
Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln	
130 135	

<210> 196
 <211> 102
 <212> PRT
 <213> Homo sapien

	<400> 196
Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr	
1 5 10 15	
Asp Met Leu Thr Glu Leu Ala Asn Phe Glu Lys Asn Val Ser Gln Ala	
20 25 30	
Ile His Lys Tyr Asn Ala Tyr Arg Lys Ala Ala Ser Val Ile Ala Lys	
35 40 45	
Tyr Pro His Lys Ile Lys Ser Gly Ala Glu Ala Lys Lys Leu Pro Gly	
50 55 60	
Val Gly Thr Lys Ile Ala Glu Lys Ile Asp Glu Phe Leu Ala Thr Gly	
65 70 75 80	
Lys Leu Arg Lys Leu Glu Lys Ile Arg Gln Asp Asp Thr Ser Ser Ser	
85 90 95	
Ile Asn Phe Leu Thr Arg	
100	

<210> 197
 <211> 138
 <212> PRT
 <213> Homo sapien

<400> 197

Glu	Ala	Asn	Glu	Val	Thr	Asp	Ser	Ala	Tyr	Met	Gly	Ser	Glu	Ser	Thr
1				5					10					15	
Tyr	Ser	Glu	Cys	Glu	Thr	Phe	Thr	Asp	Glu	Asp	Thr	Ser	Thr	Leu	Val
		20						25					30		
His	Pro	Glu	Leu	Gln	Pro	Glu	Gly	Asp	Ala	Asp	Ser	Ala	Gly	Gly	Ser
		35					40					45			
Ala	Val	Pro	Ser	Glu	Cys	Leu	Asp	Ala	Met	Glu	Glu	Pro	Asp	His	Gly
		50				55					60				
Ala	Leu	Leu	Leu	Leu	Pro	Gly	Arg	Pro	His	Pro	His	Gly	Gln	Ser	Val
65					70				75						80
Ile	Thr	Val	Ile	Gly	Gly	Glu	Glu	His	Phe	Glu	Asp	Tyr	Gly	Glu	Gly
				85				90						95	
Ser	Glu	Ala	Glu	Leu	Ser	Pro	Glu	Thr	Leu	Cys	Asn	Gly	Gln	Leu	Gly
			100				105						110		
Cys	Ser	Asp	Pro	Ala	Phe	Leu	Thr	Pro	Ser	Pro	Thr	Lys	Arg	Leu	Ser
		115					120					125			
Ser	Lys	Lys	Val	Ala	Arg	Tyr	Leu	His	Gln						
		130				135									

<210> 198
 <211> 100
 <212> PRT
 <213> Homo sapien

<400> 198

Met	Gly	Asp	Val	Lys	Asn	Phe	Leu	Tyr	Ala	Trp	Cys	Gly	Lys	Arg	Lys
1				5					10					15	
Met	Thr	Pro	Ser	Tyr	Glu	Ile	Arg	Ala	Val	Gly	Asn	Lys	Asn	Arg	Gln
		20						25					30		
Lys	Phe	Met	Cys	Glu	Val	Gln	Val	Glu	Gly	Tyr	Asn	Tyr	Thr	Gly	Met
		35				40						45			
Gly	Asn	Ser	Thr	Asn	Lys	Lys	Asp	Ala	Gln	Ser	Asn	Ala	Ala	Arg	Asp
		50				55					60				
Phe	Val	Asn	Tyr	Leu	Val	Arg	Ile	Asn	Glu	Ile	Lys	Ser	Glu	Glu	Val
65					70				75						80
Pro	Ala	Phe	Gly	Val	Ala	Ser	Pro	Pro	Pro	Leu	Thr	Asp	Thr	Pro	Asp
				85					90					95	
Thr	Thr	Ala	Asn												
			100												

<210> 199
 <211> 127
 <212> PRT
 <213> Homo sapien

<400> 199

Met	Val	Lys	Glu	Thr	Thr	Tyr	Tyr	Asp	Val	Leu	Gly	Val	Lys	Pro	Asn
1				5					10					15	

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<210> 200
<211> 90
<212> PRT
<213> Homo sapien

<400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
 1          5          10          15
His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys
          20          25          30
Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
          35          40          45
Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
          50          55          60
Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
65          70          75          80
Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
          85          90

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<210> 201
<211> 120
<212> PRT
<213> Homo sapien
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Met	Glu	Thr	Pro	Ser	Gln	Arg	Arg	Ala	Thr	Arg	Ser	Gly	Ala	Gln	Ala
1				5					10					15	
Ser	Ser	Thr	Pro	Leu	Ser	Pro	Thr	Arg	Ile	Thr	Arg	Leu	Gln	Glu	Lys
			20					25					30		
Glu	Asp	Leu	Gln	Glu	Leu	Asn	Asp	Arg	Leu	Ala	Val	Tyr	Ile	Asp	Arg
		35					40					45			
Val	Arg	Ser	Leu	Glu	Thr	Glu	Asn	Ala	Gly	Leu	Arg	Leu	Arg	Ile	Thr
	50					55					60				
Glu	Ser	Glu	Glu	Val	Val	Ser	Arg	Glu	Val	Ser	Gly	Ile	Lys	Ala	Ala
65					70					75					80
Tyr	Glu	Ala	Glu	Leu	Gly	Asp	Ala	Arg	Lys	Thr	Leu	Asp	Ser	Val	Ala
				85					90					95	
Lys	Glu	Arg	Ala	Arg	Leu	Gln	Leu	Glu	Leu	Ser	Lys	Val	Arg	Glu	Glu
			100					105					110		

Phe Lys Glu Leu Lys Ala Arg Asn
115 120

<210> 202
<211> 177
<212> PRT
<213> Homo sapien

<400> 202

Met	Ala	Ala	Gly	Val	Glu	Ala	Ala	Ala	Glu	Val	Ala	Ala	Thr	Glu	Ile
1				5					10					15	
Lys	Met	Glu	Glu	Glu	Ser	Gly	Ala	Pro	Gly	Val	Pro	Ser	Gly	Asn	Gly
			20					25					30		
Ala	Pro	Gly	Pro	Lys	Gly	Glu	Gly	Glu	Arg	Pro	Ala	Gln	Asn	Glu	Lys
		35				40						45			
Arg	Lys	Glu	Lys	Asn	Ile	Lys	Arg	Gly	Gly	Asn	Arg	Phe	Glu	Pro	Tyr
	50					55				60					
Ala	Asn	Pro	Thr	Lys	Arg	Tyr	Arg	Ala	Phe	Ile	Thr	Asn	Ile	Pro	Phe
65					70				75					80	
Asp	Val	Lys	Trp	Gln	Ser	Leu	Lys	Asp	Leu	Val	Lys	Glu	Lys	Val	Gly
				85					90					95	
Glu	Val	Thr	Tyr	Val	Glu	Leu	Leu	Met	Asp	Ala	Glu	Gly	Lys	Ser	Arg
			100					105					110		
Gly	Cys	Ala	Val	Val	Glu	Phe	Lys	Met	Glu	Glu	Ser	Met	Lys	Lys	Ala
		115					120					125			
Ala	Glu	Val	Leu	Asn	Lys	His	Ser	Leu	Ser	Gly	Arg	Pro	Leu	Lys	Val
		130				135					140				
Lys	Glu	Asp	Pro	Asp	Gly	Glu	His	Ala	Arg	Arg	Ala	Met	Gln	Lys	Ala
145					150					155				160	
Gly	Arg	Leu	Gly	Ser	Thr	Val	Phe	Val	Ala	Asn	Leu	Asp	Tyr	Lys	Val
				165					170					175	

Gly

<210> 203
<211> 164
<212> PRT
<213> Homo sapien

<400> 203

Met	Arg	Leu	Ala	Val	Gly	Ala	Leu	Leu	Val	Cys	Ala	Val	Leu	Gly	Leu
1				5					10					15	
Cys	Leu	Ala	Val	Pro	Asp	Lys	Thr	Val	Arg	Trp	Cys	Ala	Val	Ser	Glu
			20					25					30		
His	Glu	Ala	Thr	Lys	Cys	Gln	Ser	Phe	Arg	Asp	His	Met	Lys	Ser	Val
		35				40					45				
Ile	Pro	Ser	Asp	Gly	Pro	Ser	Val	Ala	Cys	Val	Lys	Lys	Ala	Ser	Tyr
	50					55					60				
Leu	Asp	Cys	Ile	Arg	Ala	Ile	Ala	Ala	Asn	Glu	Ala	Asp	Ala	Val	Thr
65					70					75				80	
Leu	Asp	Ala	Gly	Leu	Val	Tyr	Asp	Ala	Tyr	Leu	Ala	Pro	Asn	Asn	Leu
			85						90					95	
Lys	Pro	Val	Val	Ala	Glu	Phe	Tyr	Gly	Ser	Lys	Glu	Asp	Pro	Gln	Thr
			100					105						110	

Phe	Tyr	Tyr	Ala	Val	Ala	Val	Val	Lys	Lys	Asp	Ser	Gly	Phe	Gln	Met
		115					120					125			
Asn	Gln	Leu	Arg	Gly	Lys	Lys	Ser	Cys	His	Thr	Gly	Leu	Gly	Arg	Ser
	130					135					140				
Ala	Gly	Trp	Asn	Ile	Pro	Ile	Gly	Leu	Leu	Tyr	Cys	Asp	Leu	Pro	Glu
145					150					155					160
Pro	Arg	Lys	Pro												

<210> 204
 <211> 241
 <212> PRT
 <213> Homo sapien

<400> 204															
Met	Ser	Gly	Glu	Ser	Ala	Arg	Ser	Leu	Gly	Lys	Gly	Ser	Ala	Pro	Pro
1				5					10					15	
Gly	Pro	Val	Pro	Glu	Gly	Ser	Ile	Arg	Ile	Tyr	Ser	Met	Arg	Phe	Cys
			20					25					30		
Pro	Phe	Ala	Glu	Arg	Thr	Arg	Leu	Val	Leu	Lys	Ala	Lys	Gly	Ile	Arg
		35					40					45			
His	Glu	Val	Ile	Asn	Ile	Asn	Leu	Lys	Asn	Lys	Pro	Glu	Trp	Phe	Phe
	50					55					60				
Lys	Lys	Asn	Pro	Phe	Gly	Leu	Val	Pro	Val	Leu	Glu	Asn	Ser	Gln	Gly
65					70					75					80
Gln	Leu	Ile	Tyr	Glu	Ser	Ala	Ile	Thr	Cys	Glu	Tyr	Leu	Asp	Glu	Ala
				85					90					95	
Tyr	Pro	Gly	Lys	Lys	Leu	Leu	Pro	Asp	Asp	Pro	Tyr	Glu	Lys	Ala	Cys
			100					105					110		
Gln	Lys	Met	Ile	Leu	Glu	Leu	Phe	Ser	Lys	Val	Pro	Ser	Leu	Val	Gly
		115					120					125			
Ser	Phe	Ile	Arg	Ser	Gln	Asn	Lys	Glu	Asp	Tyr	Asp	Gly	Leu	Lys	Glu
	130					135					140				
Glu	Phe	Arg	Lys	Glu	Phe	Thr	Lys	Leu	Glu	Glu	Val	Leu	Thr	Asn	Lys
145					150					155					160
Lys	Thr	Thr	Phe	Phe	Gly	Gly	Asn	Ser	Ile	Ser	Met	Ile	Asp	Tyr	Leu
				165					170					175	
Ile	Trp	Pro	Trp	Phe	Glu	Arg	Leu	Glu	Ala	Met	Lys	Leu	Asn	Glu	Cys
			180					185						190	
Val	Asp	His	Thr	Pro	Lys	Leu	Lys	Leu	Trp	Met	Ala	Ala	Met	Lys	Glu
		195					200					205			
Asp	Pro	Thr	Val	Ser	Ala	Leu	Leu	Thr	Ser	Glu	Lys	Asp	Trp	Gln	Gly
	210					215					220				
Phe	Leu	Glu	Leu	Tyr	Leu	Gln	Asn	Ser	Pro	Glu	Ala	Cys	Asp	Tyr	Gly
225					230					235					240
Leu															

<210> 205
 <211> 160
 <212> PRT
 <213> Homo sapien

<400> 205

<div><210> 206</div> <div><211> 197</div> <div><212> PRT</div> <div><213> Homo sapien</div>																
<div><400> 206</div> <div>Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr</div> <div>1 5 10 15</div> <div>Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser</div> <div>20 25 30</div> <div>Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro</div> <div>35 40 45</div> <div>Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly</div> <div>50 55 60</div> <div>Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His</div> <div>65 70 75 80</div> <div>Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp</div> <div>85 90 95</div> <div>Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu</div> <div>100 105 110</div> <div>Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu</div> <div>115 120 125</div> <div>Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu</div> <div>130 135 140</div> <div>Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro</div> <div>145 150 155 160</div> <div>Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met</div> <div>165 170 175</div> <div>Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu</div> <div>180 185 190</div> <div>His His Thr Glu Gly</div> <div>195</div>																

<210> 207
 <211> 175
 <212> PRT
 <213> Homo sapien

<400> 207

Ile	Ile	Arg	Gln	Gln	Gly	Leu	Ala	Ser	Tyr	Asp	Tyr	Val	Arg	Arg	Arg		
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Leu	Thr	Ala	Glu	Asp	Leu	Phe	Glu	Ala	Arg	Ile	Ile	Ser	Leu	Glu	Thr		
			20					25					30				
Tyr	Asn	Leu	Leu	Arg	Glu	Gly	Thr	Arg	Ser	Leu	Arg	Glu	Ala	Leu	Glu		
	35					40						45					
Ala	Glu	Ser	Ala	Trp	Cys	Tyr	Leu	Tyr	Gly	Thr	Gly	Ser	Val	Ala	Gly		
50					55						60						
Val	Tyr	Leu	Pro	Gly	Ser	Arg	Gln	Thr	Leu	Ser	Ile	Tyr	Gln	Ala	Leu		
65				70					75						80		
Lys	Lys	Gly	Leu	Leu	Ser	Ala	Glu	Val	Ala	Arg	Leu	Leu	Leu	Glu	Ala		
			85					90						95			
Gln	Ala	Ala	Thr	Gly	Phe	Leu	Leu	Asp	Pro	Val	Lys	Gly	Glu	Arg	Leu		
			100					105					110				
Thr	Val	Asp	Glu	Ala	Val	Arg	Lys	Gly	Leu	Val	Gly	Pro	Glu	Leu	His		
		115				120						125					
Asp	Arg	Leu	Leu	Ser	Ala	Glu	Arg	Ala	Val	Thr	Gly	Tyr	Arg	Asp	Pro		
	130				135						140						
Tyr	Thr	Glu	Gln	Thr	Ile	Ser	Leu	Phe	Gln	Ala	Met	Lys	Lys	Glu	Leu		
145				150				155						160			
Ile	Pro	Thr	Glu	Glu	Ala	Leu	Arg	Leu	Trp	Met	Pro	Ser	Trp	Pro			
			165					170						175			

<210> 208
 <211> 177
 <212> PRT
 <213> Homo sapien

<400> 208

Met	Ala	Ala	Gly	Val	Glu	Ala	Ala	Ala	Glu	Val	Ala	Ala	Thr	Glu	Ile		
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Lys	Met	Glu	Glu	Glu	Ser	Gly	Ala	Pro	Gly	Val	Pro	Ser	Gly	Asn	Gly		
		20						25					30				
Ala	Pro	Gly	Pro	Lys	Gly	Glu	Gly	Glu	Arg	Pro	Ala	Gln	Asn	Glu	Lys		
	35				40							45					
Arg	Lys	Glu	Lys	Asn	Ile	Lys	Arg	Gly	Gly	Asn	Arg	Phe	Glu	Pro	Tyr		
50				55						60							
Ala	Asn	Pro	Thr	Lys	Arg	Tyr	Arg	Ala	Phe	Ile	Thr	Asn	Ile	Pro	Phe		
65				70					75					80			
Asp	Val	Lys	Trp	Gln	Ser	Leu	Lys	Asp	Leu	Val	Lys	Glu	Lys	Val	Gly		
			85					90						95			
Glu	Val	Thr	Tyr	Val	Glu	Leu	Leu	Met	Asp	Ala	Glu	Gly	Lys	Ser	Arg		
		100						105					110				
Gly	Cys	Ala	Val	Val	Glu	Phe	Lys	Met	Glu	Glu	Ser	Met	Lys	Lys	Ala		
	115				120							125					
Ala	Glu	Val	Leu	Asn	Lys	His	Ser	Leu	Ser	Gly	Arg	Pro	Leu	Lys	Val		
	130				135						140						
Lys	Glu	Asp	Pro	Asp	Gly	Glu	His	Ala	Arg	Arg	Ala	Met	Gln	Lys	Val		

145 150 155 160
 Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Gly Pro Gly Met
 165 170 175
 Ile

<210> 209
 <211> 196
 <212> PRT
 <213> Homo sapien

<400> 209
 Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
 1 5 10 15
 Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
 20 25 30
 Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
 35 40 45
 Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
 50 55 60
 Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
 65 70 75 80
 Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
 85 90 95
 Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
 100 105 110
 Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
 115 120 125
 Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
 130 135 140
 Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
 145 150 155 160
 Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
 165 170 175
 Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
 180 185 190
 Thr Ile Ala Arg
 195

<210> 210
 <211> 156
 <212> PRT
 <213> Homo sapien

<400> 210
 Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly Lys Glu
 1 5 10 15
 Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly Tyr Ser
 20 25 30
 Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val Gly Tyr
 35 40 45
 Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser Gly Arg
 50 55 60
 Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val Thr Gln

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<210> 211
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<212> PRT
<213> Homo sapien
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<210> 212
<211> 142
<212> PRT
<213> Homo sapien
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<div><400> 212</div>															
Glu 1	Lys	Gln	Lys	Asn 5	Lys	Glu	Phe	Ser	Gln 10	Thr	Leu	Glu	Asn	Glu 15	Lys
Asn	Thr	Leu	Leu 20	Ser	Gln	Ile	Ser	Thr 25	Lys	Asp	Gly	Glu	Leu 30	Lys	Met
Leu	Gln	Glu 35	Glu	Val	Thr	Lys	Met 40	Asn	Leu	Leu	Asn	Gln 45	Gln	Ile	Gln
Glu 50	Glu	Leu	Ser	Arg	Val	Thr 55	Lys	Leu	Lys	Glu 60	Thr	Ala	Glu	Glu	Glu
Lys 65	Asp	Asp	Leu	Glu	Glu 70	Arg	Leu	Met	Asn	Gln 75	Leu	Ala	Glu	Leu 80	Asn
Gly	Ser	Ile	Gly	Asn 85	Tyr	Cys	Gln	Asp 90	Val	Thr	Asp	Ala	Gln 95	Ile	Lys
Asn	Glu	Leu	Leu 100	Glu	Ser	Glu	Met	Lys 105	Asn	Leu	Lys	Lys	Cys 110	Val	Ser
Glu	Leu	Glu 115	Glu	Glu	Lys	Gln	Gln 120	Leu	Val	Lys	Glu 125	Lys	Thr	Lys	Val
Glu	Ser	Glu	Ile	Arg	Lys	Glu	Tyr	Leu	Glu	Lys	Ile	Gln	Gly		

130

135

140

<210> 213
 <211> 142
 <212> PRT
 <213> Homo sapien

<400> 213

Gly	Gly	Tyr	Gly	Gly	Gly	Tyr	Gly	Gly	Val	Leu	Thr	Ala	Ser	Asp	Gly
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Leu	Leu	Ala	Gly	Asn	Glu	Lys	Leu	Thr	Met	Gln	Asn	Leu	Asn	Asp	Arg
			20					25					30		
Leu	Ala	Ser	Tyr	Leu	Asp	Lys	Val	Arg	Ala	Leu	Glu	Ala	Ala	Asn	Gly
		35					40					45			
Glu	Leu	Glu	Val	Lys	Ile	Arg	Asp	Trp	Tyr	Gln	Lys	Gln	Gly	Pro	Gly
	50					55					60				
Pro	Ser	Arg	Asp	Tyr	Ser	His	Tyr	Tyr	Thr	Thr	Ile	Gln	Asp	Leu	Arg
65					70					75					80
Asp	Lys	Ile	Leu	Gly	Ala	Thr	Ile	Glu	Asn	Ser	Arg	Ile	Val	Leu	Gln
				85				90						95	
Ile	Asp	Asn	Ala	Arg	Leu	Ala	Ala	Asp	Asp	Phe	Arg	Thr	Lys	Phe	Glu
			100					105					110		
Thr	Glu	Gln	Ala	Leu	Arg	Met	Ser	Val	Glu	Ala	Asp	Ile	Asn	Gly	Leu
		115					120					125			
Arg	Arg	Val	Leu	Asp	Glu	Leu	Thr	Leu	Ala	Arg	Thr	Asp	Leu		
	130						135					140			

<210> 214
 <211> 129
 <212> PRT
 <213> Homo sapien

<400> 214

Val	Met	Arg	Val	Asp	Phe	Asn	Val	Pro	Met	Lys	Asn	Asn	Gln	Ile	Thr
1				5				10						15	
Asn	Asn	Gln	Arg	Ile	Lys	Ala	Ala	Val	Pro	Ser	Ile	Lys	Phe	Cys	Leu
			20					25					30		
Asp	Asn	Gly	Ala	Lys	Ser	Val	Val	Leu	Met	Ser	His	Leu	Gly	Arg	Pro
		35					40					45			
Asp	Gly	Val	Pro	Met	Pro	Asp	Lys	Tyr	Ser	Leu	Glu	Pro	Val	Ala	Val
	50					55					60				
Glu	Leu	Arg	Ser	Leu	Leu	Gly	Lys	Asp	Val	Leu	Phe	Leu	Lys	Asp	Cys
65					70					75					80
Val	Gly	Pro	Glu	Val	Glu	Lys	Ala	Cys	Ala	Asn	Pro	Ala	Ala	Gly	Ser
				85				90						95	
Val	Ile	Leu	Leu	Glu	Asn	Leu	Arg	Phe	His	Val	Glu	Glu	Glu	Gly	Lys
			100					105					110		
Gly	Lys	Asp	Ala	Ser	Gly	Asn	Lys	Val	Lys	Ala	Glu	Pro	Ala	Lys	Ile
		115					120					125			
Glu															

<210> 215
 <211> 148

<212> PRT

<213> Homo sapien

<400> 215

Met	Ala	Thr	Leu	Lys	Glu	Lys	Leu	Ile	Ala	Pro	Val	Ala	Glu	Glu	Glu	
1				5					10					15		
Ala	Thr	Val	Pro	Asn	Asn	Lys	Ile	Thr	Val	Val	Gly	Val	Gly	Gln	Val	
			20					25					30			
Gly	Met	Ala	Cys	Ala	Ile	Ser	Ile	Leu	Gly	Lys	Ser	Leu	Ala	Asp	Glu	
		35					40					45				
Leu	Ala	Leu	Val	Asp	Val	Leu	Glu	Asp	Lys	Leu	Lys	Gly	Glu	Met	Met	
	50					55					60					
Asp	Leu	Gln	His	Gly	Ser	Leu	Phe	Leu	Gln	Thr	Pro	Lys	Ile	Val	Ala	
65					70					75					80	
Asp	Lys	Asp	Tyr	Ser	Val	Thr	Ala	Asn	Ser	Lys	Ile	Val	Val	Val	Thr	
				85					90					95		
Ala	Gly	Val	Arg	Gln	Gln	Glu	Gly	Glu	Ser	Arg	Leu	Asn	Leu	Val	Gln	
			100					105					110			
Arg	Asn	Val	Asn	Val	Phe	Lys	Phe	Ile	Ile	Pro	Gln	Ile	Val	Lys	Tyr	
		115					120					125				
Ser	Pro	Asp	Cys	Ile	Ile	Ile	Val	Val	Ser	Asn	Pro	Val	Asp	Ile	Leu	
	130					135					140					
Thr	Tyr	Val	Thr													
145																

<210> 216

<211> 527

<212> PRT

<213> Homo sapien

<400> 216

Gln	Arg	Ala	Pro	Gly	Ile	Glu	Glu	Lys	Ala	Ala	Glu	Asn	Gly	Ala	Leu	
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Gly	Ser	Pro	Glu	Arg	Glu	Glu	Lys	Val	Leu	Glu	Asn	Gly	Glu	Leu	Thr	
			20					25					30			
Pro	Pro	Arg	Arg	Glu	Glu	Lys	Ala	Leu	Glu	Asn	Gly	Glu	Leu	Arg	Ser	
		35					40					45				
Pro	Glu	Ala	Gly	Glu	Lys	Val	Leu	Val	Asn	Gly	Gly	Leu	Thr	Pro	Pro	
	50					55					60					
Lys	Ser	Glu	Asp	Lys	Val	Ser	Glu	Asn	Gly	Gly	Leu	Arg	Phe	Pro	Arg	
65					70					75					80	
Asn	Thr	Glu	Arg	Pro	Pro	Glu	Thr	Gly	Pro	Trp	Arg	Ala	Pro	Gly	Pro	
				85					90					95		
Trp	Glu	Lys	Thr	Pro	Glu	Ser	Trp	Gly	Pro	Ala	Pro	Thr	Ile	Gly	Glu	
			100					105					110			
Pro	Ala	Pro	Glu	Thr	Ser	Leu	Glu	Arg	Ala	Pro	Ala	Pro	Ser	Ala	Val	
		115					120					125				
Val	Ser	Ser	Arg	Asn	Gly	Gly	Glu	Thr	Ala	Pro	Gly	Pro	Leu	Gly	Pro	
	130					135					140					
Ala	Pro	Lys	Asn	Gly	Thr	Leu	Glu	Pro	Gly	Thr	Glu	Arg	Arg	Ala	Pro	
145					150					155					160	
Glu	Thr	Gly	Gly	Ala	Pro	Arg	Ala	Pro	Gly	Ala	Gly	Arg	Leu	Asp	Leu	
				165					170					175		
Gly	Ser	Gly	Gly	Arg	Ala	Pro	Val	Gly	Thr	Gly	Thr	Ala	Pro	Gly	Gly	

			180					185					190				
Gly	Pro	Gly	Ser	Gly	Val	Asp	Ala	Lys	Ala	Gly	Trp	Val	Asp	Asn	Thr		
		195					200					205					
Arg	Pro	Gln	Pro	Pro	Pro	Pro	Pro	Leu	Pro	Pro	Pro	Pro	Glu	Ala	Gln		
	210					215					220						
Pro	Arg	Arg	Leu	Glu	Pro	Ala	Pro	Pro	Arg	Ala	Arg	Pro	Glu	Val	Ala		
225					230					235					240		
Pro	Glu	Gly	Glu	Pro	Gly	Ala	Pro	Asp	Ser	Arg	Ala	Gly	Gly	Asp	Thr		
			245					250						255			
Ala	Leu	Ser	Gly	Asp	Gly	Asp	Pro	Pro	Lys	Pro	Glu	Arg	Lys	Gly	Pro		
		260					265					270					
Glu	Met	Pro	Arg	Leu	Phe	Leu	Asp	Leu	Gly	Pro	Pro	Gln	Gly	Asn	Ser		
	275						280					285					
Glu	Gln	Ile	Lys	Ala	Arg	Leu	Ser	Arg	Leu	Ser	Leu	Ala	Leu	Pro	Pro		
	290					295					300						
Leu	Thr	Leu	Thr	Pro	Phe	Pro	Gly	Pro	Gly	Pro	Arg	Arg	Pro	Pro	Trp		
305					310					315					320		
Glu	Gly	Ala	Asp	Ala	Gly	Ala	Ala	Gly	Gly	Glu	Ala	Gly	Gly	Ala	Gly		
			325					330						335			
Ala	Pro	Gly	Pro	Ala	Glu	Glu	Asp	Gly	Glu	Asp	Glu	Asp	Glu	Asp	Glu		
		340					345						350				
Glu	Glu	Asp	Glu	Glu	Ala	Ala	Ala	Pro	Gly	Ala	Ala	Ala	Gly	Pro	Arg		
	355					360					365						
Gly	Pro	Gly	Arg	Ala	Arg	Ala	Ala	Pro	Val	Pro	Val	Val	Val	Ser	Ser		
	370					375					380						
Ala	Asp	Ala	Asp	Ala	Ala	Arg	Pro	Leu	Arg	Gly	Leu	Leu	Lys	Ser	Pro		
385					390				395						400		
Arg	Gly	Ala	Asp	Glu	Pro	Glu	Asp	Ser	Glu	Leu	Glu	Arg	Lys	Arg	Lys		
			405				410						415				
Met	Val	Ser	Phe	His	Gly	Asp	Val	Thr	Val	Tyr	Leu	Phe	Asp	Gln	Glu		
		420					425						430				
Thr	Pro	Thr	Asn	Glu	Leu	Ser	Val	Gln	Ala	Pro	Pro	Glu	Gly	Asp	Thr		
	435					440						445					
Asp	Pro	Ser	Thr	Pro	Pro	Ala	Pro	Pro	Thr	Pro	Pro	His	Pro	Ala	Thr		
	450					455					460						
Pro	Gly	Asp	Gly	Phe	Pro	Ser	Asn	Asp	Ser	Gly	Phe	Gly	Gly	Ser	Phe		
465					470				475						480		
Glu	Trp	Ala	Glu	Asp	Phe	Pro	Leu	Leu	Pro	Pro	Pro	Gly	Pro	Pro	Leu		
			485					490						495			
Cys	Phe	Ser	Arg	Phe	Ser	Val	Ser	Pro	Ala	Leu	Glu	Thr	Pro	Gly	Pro		
		500					505					510					
Pro	Ala	Arg	Ala	Pro	Asp	Ala	Arg	Pro	Ala	Gly	Pro	Val	Glu	Asn			
	515					520						525					

<210> 217

<211> 466

<212> DNA

<213> Homo sapien

<400> 217

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acgtccccgc	gtttcaggcc	cttggtcac	tcaatgacct	ccagttcttt	agatacaaca	180
gtaaagacag	gaagtctcag	cccatgggac	tctggagaca	ggtggaagga	atggaggatt	240

ggaagcagga	cagccaactt	cagaaggcca	gggaggacat	ctttatggag	accctgaaag	300
acatcgtgga	gtattacaac	gacagtaacg	ggtctcacgt	attgcaggga	aggtttggtt	360
gtgagatcga	gaataacaga	agcagcggag	cattctggaa	atattactat	gatggaaagg	420
actacattga	attcaacaaa	gaaatcccag	cctgggtccc	cttcga		466

<210> 218
 <211> 381
 <212> DNA
 <213> Homo sapien

<400> 218						
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tttaaagcgc	cggggtaacc	agttggagat	ctgtgccgtg	gtcctgaggc	agttgtctcc	120
acacaagtac	tacttcctcg	tgggctacag	tgaaactttg	ctgtcctact	tttaciaaatg	180
tcctgtgcga	ctccacctcc	aaactgtgcc	ctcaaagggt	gtgtataagt	acctctagaa	240
caatcccctt	ttttccatca	agctgtagcc	tgcagagaaat	ggaaacgtgg	gaaaggaatg	300
gtatgtgggg	gaaatgcata	ccctcagagg	actgaggcat	agtctctcat	ctgctattga	360
ataaagacct	tctatcttgt	a				381

<210> 219
 <211> 1293
 <212> DNA
 <213> Homo sapien

<400> 219						
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ttcaattcca	tgctgggttc	cattgtgggg	atggcactat	acacaggata	cgtcttcatg	180
ccccagcaca	tcatggcgat	attgcactac	tttgaaatcg	tacaatgacc	aagatgcgac	240
caggatcaga	ggttccttgg	ggaagaccca	ccctacgaag	ttggaatgag	accatcagat	300
gtgataagaa	actcttctag	atgtcaacat	aaccaacctt	ataaagacta	aaattcatga	360
gtagaacagg	aaaatcatcc	tgactcatgt	gttgtgttct	ttatttttaa	ttttcaaaga	420
ggctcttgta	tagcagtttt	tgtctatttt	aacattgtag	tcatttgtac	tttgatatca	480
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aactttgagt	acattttta	tgctttctat	ttttaaaact	caaaatcatt	agttgggctt	600
tactgttctt	gctattgtat	ggcatataca	tctgcctgga	tatatttcta	ctcttgacca	660
aagttttgta	aagaacaata	taagatttcg	ggtaggggta	tggggaggga	agatatttta	720
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tatctagact	ctaacagctt	ttgcttttaa	attattaaag	tgtttcttaa	tgaaaaagaa	840
aagatcttgc	taaagttaaa	ataaggaaca	tttcaccttt	taaatattta	attcttatgt	900
ggacttat	ccagaaaact	ttggtgataa	ttcttgagac	aaaagggtgt	taagtagcat	960
tattatgtaa	tgcttatata	ccatagagtt	tttaatagaa	gagaaatcca	tttcctccga	1020
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tttgcacatt	gcattaagtt	atgatgagac	gaattgttgt	taaaaattat	agcaaaaaga	1140
aatgtaaaact	tgggttaaaat	cccttcactc	tttgtattgt	tttttttaag	gtttttattc	1200
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aaaatcaaaa	aaaaaaaaaa	aaaaaaactc	gag			1293

<210> 220
 <211> 983
 <212> DNA
 <213> Homo sapien

<400> 220

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tcactgtagt	tactttcctt	gcagtggcca	aatgcccatt	aagaagggaat	acatgaccac	180
tgctgtgggg	agtcagcagg	tgcgtgatgc	agctggccac	actccatcca	cggccatgac	240
ataaaacaga	caagaagtaa	ggctggactg	taacacctca	aggcctgctc	cagtgaccca	300
ctttcttcag	agaggctcta	ccacacacac	aaccaccttc	caaattttaca	ctcagatcac	360
tacaccatgt	ctcccaagtt	aaaacatgta	tccacctaga	ctttaaatgt	gctttgtaac	420
tgttgatggc	actgtacaga	gggccaaagt	atttcccatc	agatagcatt	tttctgaacc	480
catgcctctt	gggacgagat	cacaggactt	gacccatcat	caaataggac	caggtgacct	540
acagagacat	cacaatgatg	gcttcctaca	gtcaagtcca	tttccaataa	tgctctcatc	600
taagagaacc	catgaacctt	atttgaatcc	tggttcaaac	aaaaacctta	aattatttat	660
gagacaatta	taaacttgat	agattttgat	gtgtgaaggt	atttatgaat	atttttagtc	720
agtgatggta	tactgttaag	gaaaagggtc	atatttttagg	gacaaaggct	gaaacattta	780
tggacagagt	gatatgatat	ctgggatttg	ttttaggatg	aagtgggagg	gaggaaatga	840
atggaaatag	tggtgaaaca	gtattggcca	cgagtcagct	attgtgtgct	aagacgctcc	900
tcacaccagt	ctactctgta	tgtgtttgaa	tatctctgta	ataaacttaa	caaggaaaaa	960
aaaaaaaaaa	aaaaaaactc	gag				983

<210> 221

<211> 373

<212> DNA

<213> Homo sapien

<400> 221

cattttatgg	gttaattttt	tattaaatag	caataagata	cttttataac	tcaataaaat	60
tattcaatga	tacattcgga	aaataaatgt	ataaaatatg	aaaaagtact	aaaaagcatt	120
tttcagtagt	tttaggtaag	attaatccaa	ctaaacacta	gcatatgtta	tacagtaata	180
ataaggggaa	aatacaataa	tggtgagaaa	gcaaactcaa	agcatagatc	aatgaaaaaa	240
ttgagaaatg	gacataaatg	atttagtatt	tttaaagaga	gtgaaaaatc	attatttttat	300
gcttttgtgt	agcgtagat	gaattaaata	acatatgcac	atatagcttt	gcgatacaaa	360
tttccagacc	ata					373

<210> 222

<211> 544

<212> DNA

<213> Homo sapien

<400> 222

cagagatgct	gctgctacaa	aggatcggtg	taagcagtta	acccaggaaa	tgatgacaga	60
gaaagaaaga	agcaatgtgg	ttataacaag	gatgaaagat	cgaattggaa	cattagaaaa	120
ggaacataat	gtattttcaa	acaaaataca	tgctcagttat	caagagactc	aacagatgca	180
gatgaagttt	cagcaagttc	gtgagcagat	ggaggcagag	atagctcact	tgaagcagga	240
aaatgggtata	ctgagagatg	cagtcagcaa	cactacaaat	caactggaaa	gcaagcagtc	300
tgacagaacta	aataaaactac	gccaggatta	tgctaggttg	gtgaatgagc	tgactgagaa	360
aacaggaaaag	ctacagcaag	aggaagtcca	aaagaagaat	gctgagcaag	cagctactca	420
gttgaagggtt	caactacaag	aagctgagag	aagggtggga	gaagttcaga	gctacatcag	480
gaagagaaca	gcggaacatg	aggcagcaca	gctagattta	cagagtaaata	ttgtggccaa	540
agaa						544

<210> 223

<211> 316

<212> DNA

<213> Homo sapien

<400> 223

gaggcaaggg	atatgcttta	gtgcctatta	tagttaattc	ttcaactcca	aagtctaaaa	60
cagttgaatc	tgctgaagga	aaatctgaag	aagtaaata	aacattagtt	atacccactg	120
aggaagcaga	aatggaagaa	agtggacgaa	gtgcaactcc	tgtaactgt	gaacagcctg	180
atatcttggt	ttcttctaca	ccaataaatg	aaggacagac	tgtgttagac	aagggtggctg	240
agcagtgtga	acctgctgaa	agtcagccag	aagcacttct	gagaggaaga	tgtttgcaag	300
gtaactctaa	cagttg					316

<210> 224

<211> 1583

<212> DNA

<213> Homo sapien

<400> 224

cagaccacgt	ctgccctcgc	cgctctagcc	ctgcgcecca	gcccggccgc	ggcacctccg	60
cctcgccgcc	gctaggtcgg	ccggctccgc	ccggctgccg	cctaggatga	atatcatgga	120
cttcaacgtg	aagaagctgg	cggccgacgc	aggcaccttc	ctcagtcgcg	ccgtgcagtt	180
cacagaagaa	aagcttggcc	aggctgagaa	gacagaattg	gatgctcact	tagagaacct	240
ccttagcaaa	gctgaatgta	ccaaaatatg	gacagaaaaa	ataatgaaac	aaactgaagt	300
gttattgcag	ccaaatccaa	atgccaggat	agaagaattt	gtttatgaga	aactggatag	360
aaaagctcca	agtcgtataa	acaaccacga	acttttggga	caatatatga	ttgatgcagg	420
gactgagttt	ggcccaggaa	cagcttatgg	taatgccctt	attaaatgtg	gagaaacca	480
aaaaagaatt	ggaacagcag	acagagaact	gattcaaacg	tcagccttaa	attttcttac	540
tcctttaaga	aactttatag	aaggagatta	caaaacaatt	gctaaagaaa	ggaaactatt	600
gcaaaataag	agactggatt	tggatgctgc	aaaaacgaga	ctaaaaaagg	caaaagctgc	660
agaaactaga	aattcatctg	aacaggaatt	agaataaact	caaagtgaat	ttgatcgta	720
agcagagatt	accagacttc	tgctagaggg	aatcagcagt	acacatgccc	atcaccttcg	780
ctgtctgaat	gactttgtag	aagcccagat	gacttactat	gcacagtgtt	accagtatat	840
gttggacctc	cagaaacaac	tgggaagttt	tccatccaat	tatcttagta	acaacaatca	900
gacttctgtg	acacctgtac	catcagtttt	accaaattgcg	attggttctt	ctgccatggc	960
ttcaacaagt	ggcctagtaa	tcacctctcc	ttccaacctc	agtgacctta	aggagtgtag	1020
tggcagcaga	aaggccaggg	ttctctatga	ttatgatgca	gcaaacagta	ctgaattatc	1080
acttctggca	gatgaggtga	tactgtgtt	cagtgttggt	ggaatggatt	cagactggct	1140
aatgggggaa	aggggaaacc	agaagggcaa	ggtgcccaatt	acctacttag	aactgctcaa	1200
ttaagtaggt	ggactatgga	aagggtgccc	atcatgactt	tgtatttata	tacaattaac	1260
tctaaataaa	gcaggttaag	tatcttccat	gttaatgtgt	taagagactg	aaaataaccag	1320
ccatcagaaa	ctggcctttt	tgccaataaa	gttgcatggg	aaatatattca	ttacagaatt	1380
tatgttagag	ctttcatgcc	agaatgttt	tcttacaata	ttctcttttt	attgaggttt	1440
cactaataag	cagcttctac	ttttgagcct	caacttaaa	cagaactgtt	ttttactgga	1500
tttttcatta	acagcaagct	ttttttttta	tgtaaaataa	atctattgtg	aattgaaaaa	1560
aaaaaaaaaa	aaaaaaactc	gag				1583

<210> 225

<211> 491

<212> DNA

<213> Homo sapien

<400> 225

gaacaacatc	atcttgaatc	actagataga	ctcttgacgg	aaagcaaagg	ggaaatgaaa	60
aaggaaaata	tgaagaaaga	tgaagcttta	aaagcattac	agaaccaagt	atctgaagaa	120
acaatcaagg	ttaggcaact	agattcagca	ttggaaattt	gtaaggaaga	acttgtcttg	180
catttgaatc	aattggaagg	aaataaggaa	aagtttgaaa	aacagttaaa	gaagaaatct	240
gaagaggtat	attgtttaca	gaaagagcta	aagataaaaa	atcacagtct	tcaagagact	300
tctgagcaaa	acgttattct	acagcatact	cttcagcaac	agcagcaaat	gttacaacaa	360

gagacaatta	gaaatggaga	gctagaagat	actcaaacta	aacttgaaaa	acagggtgtca	420
aaactggaac	aagaacttca	aaaacaaagg	gaaagttcag	ctgaaaagtt	gagaaaaatg	480
gaggagaaat	g					491

<210> 226

<211> 483

<212> DNA

<213> Homo sapien

<400> 226

cagccgcacg	ccgcggagca	ggggctcgga	ggtcccggga	ttacgggtgct	cgagcacgct	60
ggtgggaaag	gacccgggac	ttgaacagtg	ttgtgcggcg	ccatgcagggt	ctccagcctc	120
aatgagggtga	agattttacag	cctcagctgc	ggcaagtccc	ttcctgagtg	gcttttctgat	180
aggaagaaga	gagcgctaca	gaagaaagat	gtagatgtcc	gtaggagaaat	tgaacttatt	240
caggactttg	aaatgcctac	tgtgtgtacc	actattaagg	tgtcaaaaaga	tggacagtac	300
atttttagcaa	ctggaacata	taaacctcgg	gttcgatgtt	atgacaccta	tcaattatcc	360
ttgaagtttg	aaagggtgtt	agattcagaa	gttgtcacct	ttgaaatttt	gtctgatgac	420
tactcaaaga	ttgtcttctt	acataatgat	agatacattg	aatttcattc	gcaatcagggt	480
ttt						483

<210> 227

<211> 486

<212> DNA

<213> Homo sapien

<400> 227

gagcctcgct	aagctccgac	tctgggcggc	accgggcgtc	ccacgatgcc	gaagaacaag	60
aagcgggaaca	ctccccaccg	cggtagcagt	gctggcgggcg	gcggggtcagg	agcagccgca	120
gcgacggcg	cgacagcagg	tggccagcat	cgaaatgttc	agccttttag	tgatgaagat	180
gcatcaattg	aaacagtgag	ccattgcagt	ggttatagcg	atccttccag	ttttgctgaa	240
gatggaccag	aagtccttga	tgaggaagga	actcaagaag	acctagagta	caagttgaag	300
ggattaattg	acctaaccct	ggataagagt	gcgaagacaa	ggcaagcagc	tcttgaaggt	360
attaaaaatg	cactggcttc	aaaaatgctg	tatgaattta	ttctggaaag	gagaatgact	420
ttaactgata	gcattgaacg	ctgcctgaaa	aaaggtaaga	gtgatgagca	acgtgcagct	480
gcagcg						486

<210> 228

<211> 494

<212> DNA

<213> Homo sapien

<400> 228

gaggccagga	ctccgggaat	gcgagcaggc	cccttattct	cccagtggcc	tcgggtctgtc	60
cccacagcgg	cccggtcagg	gttgcccag	ccccaggcg	gggggcggca	ccgggggtgct	120
gaaagggaca	gaatgctttg	acctccaagc	tgtttttaaat	ctagtagata	agccagatcc	180
tgtgttgcca	taagcccttg	gccacattt	aagtgggaat	gcagctagct	tggatgtctg	240
aaactttgta	agcgcttct	gtctgaatcc	tgaacacagg	caccaagact	actgaagaag	300
ctcgtcattc	ttgtgcaggg	atagccacac	aagcaaacat	gtttgcaaaa	cttgaaagaa	360
agaaaattgc	agaaagaaga	cttgctgttc	ttaagaggcc	caggaagggtg	ctacttagga	420
atcccaccgg	cttgtgaagc	aagggaatca	agtttgctt	caatggggaa	cttgacttca	480
ggaaaatgaa	cttt					494

<210> 229

<211> 465

<212> DNA

<213> Homo sapien

<400> 229

gtcagagagc	tggtataacc	tcctggttga	catgcagAAC	cgactcaata	aggatcatcaa	60
aagcgtgggc	aagattgagc	actccttctg	gagatccttt	cacactgagc	gaaagacaga	120
accagccaca	ggcttcatcg	atggtgatct	gattgaaagt	ttcctagata	tcagccgccc	180
taagatgcag	gaggttgtgg	caaacttgca	gtatgatgat	ggcagtggta	tgaagcggga	240
ggcaactgca	gatgacctca	tcaaagtcgt	ggaggaacta	actcggatcc	attagccaag	300
gacaggatct	cttttcctga	ccctcctaaa	ggcgttgccc	tcctatcctc	ccttccttgc	360
ccacccttgg	tttctttggc	atgggaaggt	tttccttaac	cacttgccct	agagccacca	420
gtgaccttgt	gtggaaacag	ggtttttttt	acttaaaaca	gttca		465

<210> 230

<211> 495

<212> DNA

<213> Homo sapien

<400> 230

caggggaaag	ggtgtttggc	cttgaccagc	cactgctgac	ctcaatctca	gacctacaga	60
tggtgaatat	ctccctgcca	gtgttgtctc	gacccaatgc	tcaggagctt	cctagcatgt	120
accagcgctt	agggctggac	tacgaggaac	gagtgttgcc	gtccattgtc	aacgaggtgc	180
tcaagagtgt	ggtggccaag	ttcaatgcct	cacagctgat	cacccagcgg	gcccaggtat	240
ccctgttgat	ccgccgggag	ctgacagaaa	gggccaaagg	acttcagcct	catcctggat	300
gatgtggcca	tcacagactt	gagcttttagc	cgagaagtac	acaagctgcc	tgtaagaaac	360
ccaaccaagt	gggggtgaatt	ccaaaaaccc	gtgggggtga	agggcttctt	aagaatgcaa	420
ggaaggagga	aaagaattcc	atgggggggg	ggttccttaa	cccaggaaca	gggggttccc	480
ttgaattttt	ttcca					495

<210> 231

<211> 498

<212> DNA

<213> Homo sapien

<400> 231

ggcagcttct	gagaccaggg	ttgctccgtc	cgtgctccgc	ctcgccatga	cttcctacag	60
ctatcgccag	tcgtcggcca	cgctcgtcct	cggaggcctg	ggcggcggct	ccgtgcgttt	120
tgggcccggg	gtcgcttttc	gcgcgcccag	cattcacggg	ggctccggcg	gccgcggcgt	180
atccgtgtcc	tcgcgccgct	ttgtgtcctc	gtcctcctcg	gggggctacg	gcggcggcta	240
cggcggcgct	ctgaccgcgt	ccgacgggct	gctggcgggc	aacgagaagc	taacctatgca	300
gaacctcaac	gaccgcctgc	ctcctacctg	gacaaagtgc	gcgccctgga	agcgggcaac	360
ggcgaactta	gaggtgaaag	aatcccgcga	actggtacca	aaaacaaggg	gcctggggcc	420
ttccgcgact	tacagccaac	ttactacacc	gaacattcaa	gaacttgccg	gaacaaaaat	480
ttttggtgcc	accatttt					498

<210> 232

<211> 465

<212> DNA

<213> Homo sapien

<400> 232

cagggccggcc	gagtaggaaa	gctggaggcg	cgggtgggga	acatgtctga	gtcggagctc	60
ggcaggaagt	gggaccggtg	tctggcggat	gcggtcgtga	agataggtac	tggtttttgga	120
ttaggaattg	ttttctcact	taccttcttt	aaaagaagaa	tgtggccatt	agccttcggt	180

tctggcatgg	gattaggaat	ggcttattcc	aactgtcagc	atgatttcca	ggctccatat	240
cttctacatg	gaaaatatgt	caaagagcag	gagcagtgac	ttcacctgag	aacatcccag	300
cgggaggaca	agagaaaatc	atgtttattc	ctcaggaata	cttgaagtgc	cctggagtaa	360
actgccattc	ttctgtaaca	atggatatcag	taatgcttta	aactccagca	cctgggttatg	420
catttgaaac	ccaagtctgg	ttcttggttt	ggattttctc	tctgg		465

<210> 233
 <211> 366
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(366)
 <223> n = A,T,C or G

<400> 233						
cagtaaaaaa	ggttatgttt	tattaattgc	tggacaaccg	tgggaaaaca	aataagcaat	60
tgacaccacc	aaattcttat	tacattcaan	ataaaanatt	tattcacacc	acaaaaagat	120
aatcacaaca	aatatacac	taacttaaaa	aacaaaagat	tatagtga	taaaatgtta	180
tattctcttt	ttaagtgggt	aaaagtattt	tgtttgcttc	tacataaatt	tctattcatg	240
ananaataac	aatattataa	atacagtgat	agtttgcat	tcttctatag	aatgaacata	300
gacataaccc	tgaagctttt	agtttacagg	gagtttccat	gaagccacaa	actaaactaa	360
ttatca						366

<210> 234
 <211> 379
 <212> DNA
 <213> Homo sapien

<400> 234						
gagggcagcc	ctcctacctg	cgcacgtggt	gccgccgctg	ctgcctcccg	ctcgccctga	60
accagtgcc	tgcagccatg	gctcccggcc	agctcgccct	atttagtgct	tctgacaaaa	120
ccggccttgt	ggaatttgca	agaaacctga	ccgctcttgg	tttgaatctg	gtcgcttccg	180
gagggactgc	aaaagctctc	agggatgctg	gtctggcagt	cacagatgtc	tctgagttga	240
cgggatttct	gaaatgttgg	ggggacgtgt	gaaaactttg	catcctgcac	gatcccatgc	300
tggaatccta	gctcctaata	ttcagaagat	aatgcttgac	atgcgccaca	cttgattcaa	360
tcttataaca	attgttgcc					379

<210> 235
 <211> 406
 <212> DNA
 <213> Homo sapien

<400> 235						
caggctgcac	catgtacccc	accttcagtt	taaaagaaaa	aaaaaatccc	cttcactcct	60
actgggaggt	gggaccctt	tcattttcag	ttttgctcat	ctagggaaaa	taaggctttg	120
gtttccagtt	taattgtttt	tgaccttcta	aaatgttttt	atgttagcac	tgatagttgg	180
cattactggt	gttaagcact	gtgttccaga	ccgtgtctga	cttagtgtaa	cctaggagat	240
tttatagttt	tattttaatg	aaacctgat	tgacgcacag	cagtggggag	aacagcgtct	300
tttacctgtc	accgaagcca	ggaagccccg	tttgtaagcg	tgtgttgg	tgctttattg	360
tacatcctcc	agtggcgctc	tttttactct	aatgttcttt	tggttt		406

<210> 236

<211> 278
 <212> DNA
 <213> Homo sapien

<400> 236
 gagattagca cctgtgaaca atgcgttctc tgatgacact ctgagcatgg accaacgcct 60
 tcttaagcta attctgcaaa atcacatatt gaaagtaaaa gttggcctta gcgacctcta 120
 caatggacag atactggaaa ccattggagg caaacaactc cgagtctttg tgtatcggac 180
 ggctatctgc atagaaaact catgcatggt gagaggaagc aagcagggaa ggaacggtgc 240
 cattcacata ttccgagaga tcatccaacc agcagaat 278

<210> 237
 <211> 322
 <212> DNA
 <213> Homo sapien

<400> 237
 cagggccgtg gcggaggagg agcgtgcac ggtggagcgt cggggccgacc tcacctacgc 60
 ggagttcgtg cagcagtagc tgcgcccctg atcgcgagg tgcgctcctg ttcaccggcc 120
 cgtctgcccc gaccgccc aa ggccgccttc cctgacctc gcgcgcacgc gtggggctgg 180
 ggcgggcagg ctggcggtcc ggccctggccg cgactctgcc cttctttcca gaggttccgg 240
 gccctgtgct cccgcgacag gttgctgggt tcgtttgggg acagagtggg ccggtgagca 300
 ccgccaacac ctactectac ct 322

<210> 238
 <211> 613
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (399)
 <223> n=A,T,C or G

<400> 238
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 tcagcctcct tcttatcttg gtgcaagtgt ggataaactc catcaccctt tagaatttgc 120
 agacaaatct cccacacctc ctaattttacc tagcgataaa atctaccctc cttctgggtc 180
 cccgaagag aataccagca cagccaccat gacttacatg acaactactc cagcaacagc 240
 ccaaatgagc accaaggaag ccagctggga tgtggctgaa caaccaccca ctgctgattt 300
 tgctgctgcc aacttcagc gcacgcacag aactaatcgt ccccttcccc ctccgccttc 360
 ccagagatct gcagagcagc caccagttgt ggggcaggna caagcagcaa ccaatatagg 420
 attaaataat tcccacaagg ttcaaggagt agttccagtt ccagagaggc cacctgaacc 480
 tcgagccatg gatgaccctg cgtctgcctt catcagtgac agtgggtgctg ctgctgctca 540
 gtgtcccatg gctacagctg tccagccagg cctgcctgag aaagtgcggg acggtgcccg 600
 ggtcccgtg ctg 613

<210> 239
 <211> 613
 <212> DNA
 <213> Homo sapiens

<400> 239


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gaattcggca ccaggggaca ctggtgctga gctggatgat gatcagcact ggtctgacag 60
cccgtcggat gctgacagag agctgcggtt gccgtgcca gctgaggggg aagcagagct 120
ggagctgagg gtgtcggag atgaggagaa gctgcccggc tcaccgaagc accaagagag 180
aggtccctcc caagccacca gcccctccg gtctccccag gaatcagctc ttctgttcat 240
tccagtccac agcccctcaa cagagggggc ccaactccca cctgtccctg ccgccacca 300
ggagaaatca cctgaggagc gccttttccc tgagcctttg ctcccaaaag agaagcccaa 360
agctgatgcc ccctcggatc tgaaagctgt gcaactctcc atccgatcac agccagtgc 420
cctgccagaa gctaggactc ctgtctcacc agggagcccc cagccccagc caccgtggc 480
ggcctccacg ccccacca gogaggtctc cagagccttc tctctcctgt gcaaaatggc 540
aactcttaag gaaaaactca ttgcaccagt tgcggaagaa gaggcaacag ttccaaacaa 600
taagatcact gta 613

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<210> 240

<211> 585

<212> DNA

<213> Homo sapiens

<400> 240

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gaattcggca cgaggtgaga tctacgatga actttaagat tggaggtgtg acagaacgca 60
tgccaacccc agttattaaa gcttttggca tcttgaagcg agcggccgct gaagtaaacc 120
aggattatgg tcttgatcca aagattgcta atgcaataat gaaggcagca gatgaggtag 180
ctgaaggtaa attaaatgat cattttcctc tcgtgggtatg gcagactgga tcaggaactc 240
agacaaatat gaatgtaa atgaagtcatta gcaatagagc aattgaaatg ttaggaggtg 300
aacttggcag caagatacct gtgcatccca acgatcatgt taataaaagc cagagctcaa 360
atgatacttt tcccacagca atgcacattg ctgctgcaat agaagtctcat gaagtactgt 420
taccaggact acagaagtta catgatgctc ttgatgcaaa atccaaagag tttgcacaga 480
tcatcaagat tggacgtact catactcagg atgctgttcc acttactctt gggcaggaat 540
ttagtggtta tggttcaacaa gtaaaatatg caatgacaag aataa 585

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<210> 241

<211> 566

<212> DNA

<213> Homo sapiens

<400> 241

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gaattcggca ccaggcgagc tgcacctcga ggtgaaggcc tcaactgatga acgatgactt 60
cgagaagatc aagaactggc agaaggaagc ctttcacaag cagatgatgg gcggcttcaa 120
ggagaccaag gaagctgagg acggctttcg gaaggcacag aagccctggg ccaagaagct 180
gaaagaggta gaagcagcaa agaaagccca ccatgcagcg tgcaaagagg agaagctggc 240
tatctcacga gaagccaaca gcaaggcaga cccatccctc aaccctgaac agctcaagaa 300
attgcaagac aaaatagaaa agtgcaagca agatgttctt aagaccaaaag agaagtatga 360
gaagtccttg aaggaactcg accagggcac accccagtac atggagaaca tggagcaggt 420
gtttgagcag tgccagcagt tcgaggagaa acgccttcgc ttcttccggg aggttctgct 480
ggaggttcag aagcacctag acctgtccaa tgtggctggc tacaaagcca tttaccatga 540
cctggagcag agcatcagag cagctg 566

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<210> 242

<211> 556

<212> DNA

<213> Homo sapiens

<400> 242

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gaattcggca cgagcaaagg tgaagcagga catgcctccg cccgggggct atgggcccac 60
cgactacaaa cggaacttgc cgcgtcgagg actgtcgggc tacagcatgc tggccatagg 120

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gattggaacc ctgatctacg ggcactggag cataatgaag tggaaccgtg agcgcaggcg 180
cctacaaatc gaggacttcg aggctcgcat cgcgctgttg ccactgttac aggcagaaac 240
cgaccggagg accttgacaga tgcttcggga gaacctggag gaggaggcca tcatcatgaa 300
ggacgtgccc gactggaagg tgggggagtc tgtgttccac acaaccgct gggtgcccc 360
cttgatcggg gagctgtacg ggctgcgcac cacagaggag gctctccatg ccagccacgg 420
cttcatgtgg tacacgtagg ccctgtgccc tccggccacc tggatccctg cccctcccca 480
ctgggacgga ataatgctc tgcagacctg gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaaaaaaaa ctcgag                                     556

```

```

<210> 243
<211> 591
<212> DNA
<213> Homo sapiens

```

```

<400> 243
gtctatgttt gcagaaatac agatccaaga caaagacagg atgggcactg ctggaaaagt 60
tattaaatgc aaagcagctg tgctttggga gcagaagcaa cccttctcca ttgaggaaat 120
agaagttgcc ccaccaaaga ctaaagaagt tcgcattaag attttggcca caggaatctg 180
tcgcacagat gaccatgtga taaaaggaac aatggtgtcc aagtttccag tgattgtggg 240
acatgaggca actgggattg tagagagcat tggagaagga gtgactacag tgaaaccagg 300
tgacaaagtc atccctctct ttctgccaca atgtagagaa tgcaatgctt gtcgcaaccc 360
agatggcaac ctttgcatta ggagcgatat tactggtcgt ggagtactgg ctgatggcac 420
caccagattht acatgcaagg gcaaaccagt ccaccacttc atgaacacca gtacatttac 480
cgagtacaca gtgggtggatg aatcttctgt tgctaagatt gatgatgcag ctctctctga 540
gaaagtctgt ttaattggct gtgggttttc cactggatat ggcgctgctg t                                     591

```

```

<210> 244
<211> 594
<212> DNA
<213> Homo sapiens

```

```

<400> 244
gaattcggca cgagaacaga gtgaactgag catcagtcag aaaaagtcta tgtttgcaga 60
aatacagatc caagacaaag acaggatggg cactgctgga aaagttatta aatgcaaagc 120
agctgtgctt tgggagcaga agcaaccctt ctccattgag gaaatagaag ttgccccacc 180
aaagactaaa gaagttcgca ttaagatttt ggccacagga atctgtcgca cagatgacca 240
tgtgataaaa ggaacaatgg tgtccaagtt tccagtgatt gtgggacatg aggcaactgg 300
gattgtagag agcattggag aaggagtgcac tacagtgaac ccaggtgaca aagtcacccc 360
tctctttctg ccacaatgta gagaatgcaa tgcttgtcgc aaccagatg gcaacctttg 420
cattaggagc gatattactg gtcgtggagt actggctgat ggcaccacca gatttacatg 480
caagggcaaa ccagtccacc acttcatgaa caccagtaca tttaccgagt acacagtggg 540
ggatgaatct tctgttgcta agattgatga tgcagctcct cctgagaaag tctg                                     594

```

```

<210> 245
<211> 615
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (105)
<223> n=A,T,C or G

```

```

<400> 245

```

```

gtccctttcc tctgctgccg ctccggtcacg cttgtgcccc aaggaggaaa cagtgcacaga 60
cctggagact gcagttctct atccttccac agctctttca ccatnctgga tcacttcctt 120
tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctattttc 180
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tgggtgtagat gctggaaagt 240
ataccattgg cttgggccag gccaaagatg gcttctgcac agatagagaa gatattaact 300
ctctttgcat gactgtgggt cagaatctta tggagagaaa taacctttcc tatgattgca 360
ttggggcggt ggaagttgga acagagacaa tcatcgacaa atcaaagtct gtgaagacta 420
atgtgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca gctgctgtct tcaatgcttg ttaactggat tgagtccagc 540
tcttgggatg gacggtatgc cctggtaagt tgcaggagat attgctgtat atgccacagg 600
aaatgctaga cctac 615

```

<210> 246

<211> 546

<212> DNA

<213> Homo sapiens

<400> 246

```

gaattcggca ccaggctgcc tcccgtctgc cctgaaccca gtgcctgcag ccatggctcc 60
cggccagctc gccttattta gtgtctctgc aaaaccggcc ttgtgaattt gcaagaaacc 120
tgaccgctct tggtttgaat ctggctcgtt ccggaggggac tgcaaaagct ctccagggatg 180
ctggctctggc agtcagagat gtctctgagt tgacgggatt tcctgaaatg ttgggggggac 240
gtgtgaaaac tttgcactct gcagtcctat ctggaatcct agctcgtaat attccagaag 300
ataatgctga catggccaga cttgatttca atcttataag agttgttgcc tgcaatctct 360
atccctttgt aaagacagtg gcttctccag gtgtaactgt tgaggaggct gtggagcaaa 420
ttgacattgg tggagtaacc ttactgagag ctgcagccaa aaaccacgct cgagtgcagc 480
tgggtgtgtga accagaggac tatgtgggtg ggtgtccacg gagatgcaga gctccgagag 540
taagga 546

```

<210> 247

<211> 564

<212> DNA

<213> Homo sapiens

<400> 247

```

gaattcggca ccagagatca cgtgcagtga gatgcagcaa aaagttgaac ttctgagata 60
tgaatctgaa aagcttcaac aggaaaattc tattttgaga aatgaaatta ctactttaaa 120
tgaagaagat agcatttcta acctgaaatt agggacatta aatggatctc aggaagaaat 180
gtggcaaaaa acggaaactg taaaacaaga aaatgctgca gttcagaaga tggttgaaaa 240
tttaaagaaa cagatttcag aattaaaaat caaaaaccaa caattggatt tggaaaatac 300
agaacttagc caaaagaact ctcaaaacca ggaaaaactg caagaactta atcaacgtct 360
aacagaaatg ctatgccaga aggaaaaaga gccaggaaac agtgcattgg aggaacggga 420
acaagagaag tttaatctga aagaagaact ggaacgttgt aaagtgcagt cctccacttt 480
agtgtcttct ctggaggcgg agctctctga agttaaata cagacccata ttgtgcaaca 540
ggaaaaccac cttctcaaag atga 564

```

<210> 248

<211> 434

<212> DNA

<213> Homo sapiens

<400> 248

```

gttcttgttt gtggatcgct gtgatcgta cttgacaatg cagatcttcg tgaagactct 60
gactggtaag accatcaccc tcgagggtga gcccagtgac accatcgaga atgtcaaggc 120

```

```

aaagatccaa gataaggaag gcatccctcc tgaccagcag aggctgatct ttgctggaaa 180
acagctggaa gatgggcgca cctgtctga ctacaacatc cagaaagagt ccaccctgca 240
cctggtgctc cgtctcagag gtgggatgca aatcttcgtg aagacactca ctggcaagac 300
catcaccctt gaggtggagc ccagtgcac catcgagaac gtcaaagcaa agatccagga 360
caaggaaggc attcctcctg accagcagag gttgatcttt gccggaaagc cagcctggga 420
agatggggcc gccca 434

```

```

<210> 249
<211> 416
<212> DNA
<213> Homo sapiens

```

```

<400> 249
gcgggcccag gaggcggcgg cggcggcggc ggacgggccc cccgcggcag acggcgagga 60
cggacaggac ccgcacagca agcacctgta cacggccgac atgttcacgc acgggatcca 120
gagcgccgcg cacttcgtca tgttcttcgc gccctggtgt ggacactgcc agcggctgca 180
gccgacttgg aatgacctgg gagacaaata caacagcatg gaagatgcca aagtctatgt 240
ggctaaagtg gactgcacgg cccactccga cgtgtgctcc gcccgagggg tgcgaggata 300
ccccacctta aagcttttca agccaggcca agaagctgtg aagtaccagg gtcctcggga 360
cttcagaca ctggaaaact ggatgctgca gacactgaac gaggagccag tgacac 416

```

```

<210> 250
<211> 504
<212> DNA
<213> Homo sapiens

```

```

<400> 250
gaattcggca cgaggcgggt aacgttatag tatttgtcag aagttggggg ctccgtgggc 60
attgtgatcc gtcccaggca gtggattagg aggccagaag gagatccctt ccacggtgct 120
aggctgagat ggatcctctc agggcccaac agctggctgc ggagctggag gtggagatga 180
tgcccgatat gtacaacaga atgaccagt cctgccaccg gaagtgtgtg cctcctcact 240
acaaggaagc agagctctcc aagggcgagt ctgtgtgcct ggaccgatgt gtctctaagt 300
acctggacat ccatgagcgg atgggcaaaa agttgacaga gttgtctatg caggatgaag 360
agctgatgaa gaggggtgcag cagagctctg ggctgcatg aggtccctgt cagtatacac 420
cctgggggtgt accccacccc tcccacttt aataaacgtg ctccctgttg ggtgtcatct 480
gtgaagactg ccaggcctag ctct 504

```

```

<210> 251
<211> 607
<212> DNA
<213> Homo sapiens

```

```

<400> 251
gatgaaaata cacaatttta ctagcaaattg cctctactgt aatcgctatt taccacaga 60
tactctgctc aaccatatgt taattcatgg tctgtcttgt ccatattgcc gttcaacttt 120
caatgatgtg gaaaagatgg ccgcacacat gcggatggtt cacattgatg aagagatggg 180
acctaaaaca gattctactt tgagttttga tttgacattg cagcagggta gtcacactaa 240
catccatctc ctggttaacta catacaatct gagggatgcc ccagctgaat ctgttgctta 300
ccatgcccac aataatcctc cagttcctcc aaagccacag ccaaaggttc aggaaaaggc 360
agatatccct gtaaaaagtt cacctcaagc tgcagtgcc tataaaaaag atgttgggaa 420
aaccctttgt cctcttttgc tttcaatcct aaaaggacc atatctgatg cacttgcaca 480
tcacttacga gagaggcacc aagttattca gacggttcat ccagttgaga aaaagctcac 540
ctacaaatgt atccattgcc ttggtgtgta taccagcaac atgaccgcct caactatcac 600
tctgcat 607

```

<210> 252
 <211> 618
 <212> DNA
 <213> Homo sapiens

<400> 252
 gaattcgcac caggggtcct gctgggtcttc gcctttcttc tccgcttcta ccccgtcggc 60
 cgctgccact ggggtccctg gccccaccga catggcgggc gtgttgagca agtcctggag 120
 cgcacggagc tgaacaagct gcccaagtct gtccagaaca aacttgaaaa gtcccttgct 180
 gatcagcaat ccgagatcga tggcctgaag gggcgggcatg agaaatttaa ggtggagagc 240
 gaacaacagt attttgaaat agaaaagagg ttgtcccaca gtcaggagag acttgtgaat 300
 gaaacccgag agtgtcaaag cttgcgggctt gagctagaga aactcaacaa tcaactgaag 360
 gcactaactg agaaaaacaa agaacttgaa attgctcagg atcgcaatat tgccattcag 420
 agccaattta caagaacaaa ggaagaatta gaagctgaga aaagagactt aattagaacc 480
 aatgagagac tatctcaaga acttgaatac ttaacagagg atgttaaacg tctgaatgaa 540
 aaacttaaag aaagcaatac aacaaagggt gaacttcagt taaaattgga tgaacttcaa 600
 gcttctgatg tttctggt 618

<210> 253
 <211> 1201
 <212> DNA
 <213> Homo sapiens

<400> 253
 gaattcggca ccaggggtggc gagcgcggct gctgtgctgg ggcgagcagc ggggaccgtg 60
 tgtgagtttg gcatgatttg gtcccctggg attctgcctt agcaagaaag aagttggaaa 120
 tacttcctgg aagaaaacta aaacaataca aaagccacag ctatttgatt gcatgtcagc 180
 ccccttaciaa atatggacac atttcctagc ctatttccac ctggaggaga tagtaggctg 240
 aatcctgagc ctgagttcca aaatatgtta attgatgaaa ggggtacgctg tgaacatcat 300
 aaacataatt atcaggctct gaaaattgaa caaaaagggt tgcaggaaga atatgtaaaa 360
 tcacaaaatg aacttaaacg tgtattaatt gaaaagcaag caagccagga aaaattccaa 420
 ctgctccttg aagacttaag gggagaatta gtagagaaag ctagagacat agaaaaaatg 480
 aaactgcagg tactaacacc acaaaaattg gaattggtaa aagcccaact acaacaagaa 540
 ttagaagctc caatgcgaga acgttttcgg actcttgatg aagaagtgga aaggtacaga 600
 gctgagtata acaagctgcg ctacgagtat acatttctca agtcagagtt tgaacaccag 660
 aaagaagagt ttactcgggt ttcagaagaa gagaaaatga aatacaagtc agaggttgca 720
 cgactggaga aggacaaaga ggagctacat aaccagctgc ttagtggtga tcccacgaga 780
 gacagcaaac gaatggagca acttggtcga gaaaaaacc atttgcttca gaaattgaaa 840
 agtttagagg ctgaagtagc agaattaagg gctgagaaag aaaattctgg tgctcaggta 900
 gaaaatgtcc aaagaataca ggtgaggcag ttggctgaga tgcaggctac actcagatcc 960
 ttggaggctg aaaagcagtc agctaaacta caagctgagc gtttagaaaa agaactacia 1020
 tcaagcaatg aacagaatac ctgcttaatc agcaaactgc atagagctga ccgagaaatc 1080
 agcacactgg ccagtgaagt gaaagagctt aaacatgcaa acaaactaga aataactgac 1140
 atcaaactgg aggcagcaag agctaagagt gagctcgaaa gagaaaggaa taagatccaa 1200
 a 1201

<210> 254
 <211> 560
 <212> DNA
 <213> Homo sapiens

<400> 254
 gaattcggca ccagtttggg ggggtgaggtt taattggaaa tggctctctg ggactgaaaa 60

```

ctgatgtttt tgcagattac ctcagggaaa cggagggtttg ttgagttaca gacacattaa 120
accaaaggcc gtgggaaaac ccctctccag ctccagggga ttggtcagga ccacccacta 180
accagtgcct tccttcttaa cattcacttt tagcagcttg tgtttatttt acatgggcag 240
ttttgatggg aaattgccat gaccacaggg gtttgaggtt ctgctttttt ttttcttct 300
tctttttcgg gggactgggg gactcctccc aagatcacat tttagcatct ttctctccta 360
ctccatttag aaaaataagt aacaggtgaa atgtggtctc agtgtaaacg ggataattct 420
gctaccggct cctccctgat gattctgaaa tacactactg aacgagctct ggctggctct 480
ttctatcctg gatgtggttc ttctgtgtag caattccttg atgtccagtt tggaaagatg 540
tactcttctc aacaagaaaa                                     560

```

```

<210> 255
<211> 612
<212> DNA
<213> Homo sapiens

```

```

<400> 255
gaattcggca ccaggcgggg cagcagggcc gcggccatgg ggagcttgaa ggaggagctg 60
ctcaaagcca tctggcacgc cttcaccgac tcgaccagga ccacagggca aggtctccaa 120
gtcccagctc aaggtecttt ccataacct gtgcacgggt ctgaagggtc ctcagacctc 180
agttgccctt gaagagcact tcagggatga tgatgaggtt ccagtgtcca accagggcta 240
catgccttat ttaaacaggt tcatttttga aaagggtcca gacaactttg acaagattga 300
attcaatagg atgtgttgga ccctctgtgt caaaaaaaaa cctcacaag aatcccctgc 360
tcattacaga agaagatgca tttaaaatat ggggtatttt caacttttta tctgaggaca 420
agtatccatt aattattgtg tcagaagaga ttgaatacct gcttaagaag cttacagaag 480
ctatgggagg aggttggcag caagaacaat ttgaacatta taaaatcaac tttgatgaca 540
gtaaaaatgg cttttctgca tgggaactta ttgagcttat tggaaatgga cagtttagca 600
aaggcatgga cc                                     612

```

```

<210> 256
<211> 1132
<212> DNA
<213> Homo sapiens

```

```

<400> 256
gaattcggca cgaggctctgg gagaggcctc tggagcagga ggcccagtg ctcttctgac 60
ccaaggcccc gccgtccagc ttctaagtgc cagatgatgg aggagcgtgc caacctgatg 120
cacatgatga aactcagcat caagggtgtt ctccagtcgg ctctgagcct gggccgcagc 180
ctggatgcgg accatgcccc cttgcagcag ttctttgtag tgatggagca ctgcctcaaa 240
catgggctga aagttaagaa gagttttatt ggccaaaata aatcattctt tggctctttg 300
gagctgggtg agaaactttg tccagaagca tcagatatag cgactagtgt cagaaatctt 360
ccagaattaa agacagctgt gggaagagge cgagcgtggc tttatcttgc actcatgcaa 420
aagaaactgg cagattatct gaaagtgtt atagacaata aacatctctt aagcgagttc 480
tatgagcctg aggctttaat gatggaggaa gaagggtatg tgattgttgg tctgctggtg 540
ggactcaatg ttctcgatgc caatctctgc ttgaaaggag aagacttgga ttctcaggtt 600
ggagtaatag atttttccct ctaccttaag gatgtgcagg atcttgatgg tggcaaggag 660
catgaaagaa ttactgatgt ccttgatcaa aaaaattatg tggaagaact taaccggcac 720
ttgagctgca cagttgggga tcttcaaacc aagatagatg gcttggaata gactaactca 780
aagcttcaag aagagctttc agctgcaaca gaccgaattt gctcacttca agaagaacag 840
cagcagttaa gagaacaaaa tgaattaatt cgagaaagaa gtgaaaagag tgtagagata 900
acaaaacagg ataccaaagt tgagctggag acttacaagc aaactcggca aggtctggat 960
gaaatgtaca gtgatgtgtg gaagcagcta aaagaggaga agaaagtccg gttggaactg 1020
gaaaaagaac tggagttaca aattggaatg aaaccgaaa tggaaattgc aatgaagtta 1080
ctggaaaagg acaccacaga gaagcaggac acactagttg ccctccgcca gc 1132

```

<210> 257
 <211> 519
 <212> DNA
 <213> Homo sapiens

<400> 257
 gaattcgtga cacgaggtgc tcgagatgaa cccagcgcc cccagctacc ccatggcctc 60
 tctgtacgtg ggggacctgc accccgacgt gaccgaggcg atgctctacg agaagttcag 120
 cccggccggg cccatcctct ccatccgggt ctgcaggagc atgatcacc gccgctcctt 180
 gggctacgcy tacgtgaact tccagcagcc ggcggacgcy gaacgtgctt tggacaccat 240
 gaattttgat gttataaagg gcaagccagt acgcatcatg tggctctcagc gtgatccatc 300
 acttcgcaaa agtggagtag gcaacatatt cattaaaaat ttggacaaat ccatcgacaa 360
 taaagcacta tatgatacgt tttctgcgtt tggtaacatc ctttcatgta aggtgggtttg 420
 tgatgaaaat ggctccaagg gctatggatt tgtacacttt gaaacacagg aagcagctga 480
 aagagctatt gaaaaaatga atgggatgct tctaaatga 519

<210> 258
 <211> 596
 <212> DNA
 <213> Homo sapiens

<400> 258
 gctttgccaa agacttagaa gctaagcaga aaatgagctt aacatcctgg tttttggtga 60
 gcagtggagg cactcgccac aggtcgccac gagaaatgat ttttggttga agagatgact 120
 gtgagctcat gttgcagctc cgtagtgtgg ataagcaaca cgctgtcatc aactatgatg 180
 cgtctacgga tgagcattta gtgaaggatt tgggcagcct caatgggact tttgtgaatg 240
 atgtaaggat tccggaacag acttatatca ccttgaaact tgaagataag ctgagatttg 300
 gatatgatac aaatcttttc actgtagtac aaggagaaat gaggggtccct gaagaagctc 360
 ttaagcatga gaagtttacc attcagcttc agttgtccca aaaatcttca gaatcagaat 420
 tatccaaatc tgcaagtgcc aaaagcatag attcaaagg agcagacgct gctactgaag 480
 tgcagcacia aactactgaa gcactgaaat ccgaggaaaa agccatggat atttctgcta 540
 tgccccgtgg tactccatta tatgggcagc cgtcatggtg gggggatgat gaggtg 596

<210> 259
 <211> 595
 <212> DNA
 <213> Homo sapiens

<400> 259
 gaattcggca ccagagaaaa agcttcaagg tatattgagt cagagtcaag ataaatcact 60
 tcggagaatt tcagaattaa gagaggagct gcaaattggac cagcaagcaa agaaacatct 120
 tcaggacgag tttgatgcat gtttggagga gaaagatcag tatatcagtg ttctccagac 180
 tcaggtttct cttctaaagc agcgattaca gaatggccca atgaatggtg atgctcccaa 240
 accctccct cccggggagc tccaggcaga agtgcacggt gacacggaga agatggaggg 300
 cgtcggggaa ccagtgggag gtgggacttc cgctaaaacc ctggaaatgc tccagcaaag 360
 agtgaaacgt caggagaatc tgcttcagcg ctgtaaggag acaattgggt cccacaagga 420
 gcagtgcgca ctgctgctga gtgagaagga ggcactgcag gagcagttgg atgaaaggct 480
 gcaggagctg gaaaagatga aggggatggg aataaccgag acgaagcggc aaatgcttga 540
 gaccctggaa ctgaaagaag atgaaattgc tcagcttcgt agtcatatca aacag 595

<210> 260
 <211> 994
 <212> DNA
 <213> Homo sapiens

<400> 260

```

gaattcggca cgaggcggtg cctgccttct tgctgtctat cagcctttct tgcctcttcc 60
ttttcgcctt cctgtttctt cccttttctca aacaaacaag acatggcaaa ccgcagtcta 120
accagccctt ttgaaattat ccatagtttt acagacagct ccaggccatg agccacaatg 180
tccaaaatta ttcttgagca ctgatataaa ttacttagac cttctttgag ggcagaactc 240
agctgttgct ctcatgatgg gcagtgtggt aaagggttct ggtatgtctt caaaatgagt 300
ccacgagttt actgagtgtc tacaggtaaa ggaatgaata taagatgtct ttctgatcag 360
aacagggtgc ctttcacatg agctttacta gactctggga gggaaaagta gccaaagtact 420
tctgaaccat tttttaatac ttgttttgct atgggtgaaat tatagcagtt atcccaaaat 480
gtttttaatta tcaaaatact gtctttttaa aaaaaaaaaa agtaacacct tttaaagcat 540
tagatttcac ttgggtttct tttccaaaaa atgctaggta gacaaggcat tgtaaacaatg 600
agtttccttt aagaaccatc agaataataa ttttaacatga agaaaactgc tataatctagt 660
agaaataata tctaaagttt aacaactaaa gtaccctcac agaataagcaa atacccttct 720
gttctggaca tgggttcaaa tttgaatatg gaaataattt ccttggaagt ccctagaggc 780
aggtcagagg aagtatgcat taagagggaagg gagagagaat ggaaataaaa gtcactataa 840
tgcagattta tgccttattt ttttagcattt tttaaatgtt gggcttttca aggtgttttt 900
tgctttttat tagatctata taaataagtt aactagcaat ttagttttgt atttaagcta 960
cacttaatct ttttctttgg tgatatttat ttct 994

```

<210> 261

<211> 594

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (538)

<223> n=A,T,C or G

<400> 261

```

gaattcggca ccagtggaga tccagctgaa ccatgccaac cgccaggctg cggaggcaat 60
caggaacctt cggaacaccc agggaaatgct gaaggacaca cagctgcacc tggacgatgc 120
tctcagaggc caggacgacc tgaaagagca gctggccatg gttgagcgca gagccaacct 180
gatgcaggct gagatcgagg agctcagggc atccctggaa cagacagaga ggagcaggag 240
agtggccgag caagagctac tggatgccag tgagcgctg cagctcctcc acaccagaa 300
caccagcctc atcaacacca agaagaagct ggagacagac atttcccaa tccagggaga 360
gatggaagac atcgtccagg aagcccgcga cgcagaagag aaggccaaga aagccatcac 420
tgatgccgcc atgatggcgg agggagctgaa gaaggagcag gacaccagcg cccacctgga 480
gcggatgaag aagaacatgg agcagaccgt gaaggacctg cagcaccgtc tggacgancg 540
tgagcagctt ggcgctgaag ggcgggcaag aagcagatcc agaaactgga ggct 594

```

<210> 262

<211> 594

<212> DNA

<213> Homo sapiens

<400> 262

```

gaaaagggtg ctggagccaa aggcatagtc agggttaatg ctcttttttc tttatcccaa 60
atcagatagt gtttaggctt tttcatcaaa tataaaaacc cagcccagtt catggctcat 120
tcggcagcaa ccctgagacg ctttacagct ctagacccta aaagggtcaa aggccgtctt 180
atgctcaata tacattttat tacccaatct gccccggaca ttaaataaaa ctccaaaaat 240
taaatacggc cctcaaacc cacaacagga cttaattgac ctacacttca aggtgtagaa 300
taataaaaaa aaaaagttgc aattccttgc ctccgctgtg agacaaacc cagccacatc 360

```



```

tccagcacac aagaacttcc aaacgcctga accacagcag ccaggcggtc ctccagaacc 420
tcctcccccga ggagcttgct acatgtgccg gaaatctggc cactaggcca aggaatgcct 480
gcagccccgg attcctccta agccgtgtcc catctgtgcg ggacccccact gaaaatcgga 540
ctgttcaact cacctggcag ccactctcag agaccctgga actctggccc aagg          594

```

```

<210> 263
<211> 506
<212> DNA
<213> Homo sapiens

```

```

<400> 263
gaattcggca cgagcggaaa cttaggggcc acgtgagcca cggccacggc cgcataggca 60
agcaccggaa gcacccccggc ggccgcggta atgctgggtg tctgcatcac caccggatca 120
acttcgacaa ataccaccca ggctactttg ggaaagttgg tatgaagcat taccacttaa 180
agaggaaacca gagcttctgc ccaactgtca accttgacaa attgtggact ttggtcagtg 240
aacagacacg ggtgaatgct gctaaaaaca agactggggc tgctcccatc attgatgtgg 300
tgcgatcggg ctactataaa gttctgggaa agggaaagct cccaaagcag cctgtcatcg 360
tgaaggccaa attcttcagc agaagagctg aggagaagat taagagtgtt gggggggcct 420
gtgtcctggt ggcttgaagc cacatggagg gagtttcatt aaatgctaac tactttttta 480
aaaaaaaaaa aaaaaaaaaa ctcgag          506

```

```

<210> 264
<211> 600
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (32)
<223> n=A,T,C or G

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<400> 264
ggctcgtgaa cacacactga cagctatagg gnaggcggcg gcaccgtccc cgcttcccct 60
cggcggcggg gtgtcccgtc ggccggccctg aagtgaccca taaacatgct ttgtgagagg 120
aaaggcctct cggagctgcg atcggagctc tacttcctca tcgcccgggt cctggaagat 180
ggaccctgtc agcaggcggc tcaggtgctg atccgcgagg tggccgagaa ggagctgctg 240
ccccggcgca ccgactggac cgggaaggag catcccagga cctaccagaa tctgggtgaag 300
tattacagac acttagcacc tgatcacttg ctgcaaatat gtcactgact aggacctctt 360
cttgaacaag aaattcctca aagtgttcct ggagtacaaa ctttattagg agctggaaga 420
cagtctttac tacgcacaaa taaaagctgc aagcatgttg tgtggaaagg atctgctctg 480
gctgcgttgc actgtggaag accacctgag tcaccagtta actatggtag cccacccagc 540
attgcggata ctctgttttc aaggaagctg aatgggaaat acagacttga gcgacttggt 600

```

```

<210> 265
<211> 534
<212> DNA
<213> Homo sapiens

```

```

<400> 265
gaattcggca cgagtgagga gcccatcatg gcgacgcccc ctaagcggcg ggcggtggag 60
gccacggggg agaaagtgtc gcgctacgag accttcatca gtgacgtgct gcagcgggac 120
ttgcgaaagg tgctggacca tcgagacaag gtatatgagc agctggccaa ataccttcaa 180
ctgagaaatg tcattgagcg actccaggaa gctaagcact cggagtata tatgcagggt 240
gatttgggct gtaacttctt cgttgacaca gtggtcccag atacttcacg catctatgtg 300

```

```

gccctgggat atggtttttt cctggagttg aacttggcag aagctctcaa gttcattgat 360
cgtaagagct ctctcctcac agagctcagc aacagcctca ccaaggactc catgaatatc 420
aaagcccata tccacatggt gctagagggg cttagagaac tacaaggcct gcagaatttc 480
ccagagaagc ctcaccattg acttcttccc cccatcctca gacattaaag agcc          534

```

```

<210> 266
<211> 552
<212> DNA
<213> Homo sapiens

```

```

<400> 266
gaattcggca ccaggggcacc tccgcctcgc cgccgctagg tcggccggct ccgcccggct 60
gccgcctagg atgaatatca tggacttcaa cgtgaagaag ctggcggccg acgcaggcac 120
cttcctcagt cgcgcctgct agttcacaga agaaaagctt ggccaggctg agaagacaga 180
attggatgct cacttagaga acctccttag caaagctgaa tgtacaaaaa tatggacaga 240
aaaaataatg aaacaaactg aagtgttatt gcagccaaat ccaaagtcca ggatagaaga 300
atttgtttat gagaaactgg atagaaaagc tccaagtcgt ataaacaacc cagaactttt 360
gggacaatat atgattgatg cagggactga gtttggccca ggaacagctt atggtaatgc 420
ccttattaaa tgtggagaaa cccaaaaaag aattggaaca gcagacagag aactgattca 480
aacgtcagcc ttaaattttc ttactccttt aagaaacttt atagaaggag attacaaaac 540
aattgctaaa ga          552

```

```

<210> 267
<211> 551
<212> DNA
<213> Homo sapiens

```

```

<400> 267
gaagcctacc agccagggtgc cgcccccccc acccccggcc cagccccctc ctgcagcgggt 60
ggaagcggct cggcagatcg agcgtgaggc ccagcagcag cagcacctgt accgggtgaa 120
catcaacaac agcatgcccc caggacgcac gggcatgggg accccgggga gccagatggc 180
ccccgtgagc ctgaatgtgc cccgacccaa ccagggtgagc gggcccgtca tgcccagcat 240
gcctcccggg cagtggcagc aggcgcctct tccccagcag cagcccatgc caggcttgcc 300
caggcctgtg atatccatgc agggccaggc ggccgtggct gggccccgga tgcccagcgt 360
gcagccaccc aggagcatct caccagcgc tctgcaagac ctgctgcgga ccctgaagtc 420
gccagctcc cctcagcagc aacagcaggt gctgaacatt ctcaaataca acccgcagct 480
aatggcagct ttcatacaac agcgcacagc caagtacgtg gccaatcagc ccggcatgca 540
gccccagcct g          551

```

```

<210> 268
<211> 573
<212> DNA
<213> Homo sapiens

```

```

<400> 268
gaattcggca ccaggggttcc ttgtgggcta gaagaatcct gcaaaaatgt ctctctatcc 60
atctctcgaa gacttgaagg tagacaaagt aattcaggct caaactgctt tttctgcaaa 120
ccctgccaat ccagcaattt tgtcagaagc ttctgctcct atccctcacg atggaaatct 180
ctatcccaga ctgtatccag agctctctca atacatgggg ctgagtttaa atgaagaaga 240
aatacgtgca aatgtggccg tggtttctgg tgcaccactt caggggcagt tggtagcaag 300
accttccagt ataaactata tgggtggctcc tgtaactggg aatgatgttg gaattcgtag 360
agcagaaatt aagcaaggga ttcgtgaagt cattttgtgt aaggatcaag atggaaaaat 420
tggtactcag cttaaataca tagataatgg tatatttgtt cagctagtcc aggctaattc 480
tccagcctca ttggttggtc tgagatttgg ggaccaagta cttcagatca atggtgaaaa 540

```

ctgtgcagga tggagctctg ataaagcgca caa

573

<210> 269

<211> 500

<212> DNA

<213> Homo sapiens

<400> 269

gaatcggcac	caggaaacct	ttattagcag	agatagctgg	cttggatcag	attacgggga	60
atgtggggga	gccatgaaga	aactaactaa	aggggagcct	ttggggacca	gggggagaca	120
agtcactatt	ttgagggaga	aagctctgga	ttgattctga	caggacactt	gagtgtgaac	180
tgtccaagct	aagcctctgg	gtgtgtagag	agagccctta	cagatagata	gcacctttgc	240
tttcagagtg	gaaggactag	ccactaagga	ccagaccaag	atgcatgtag	gtcactgaca	300
agcacctgat	gaagaggagg	ggtctcctcc	aagtttgtgt	ttggaactcc	tcctgtgttc	360
aatttcctaa	aagccataat	ccagcaagct	gaactcatga	gaaggctctgc	ttcatgttga	420
gcatggaaga	cagaacacag	acggaaactg	cagtgatggg	gtgaagacac	cacggatagg	480
ttaggggcag	tgaggaggaa					500

<210> 270

<211> 224

<212> DNA

<213> Homo sapiens

<400> 270

gaattcggca	cgagaagact	acaatctcca	gggaaacctg	gggcgtctcg	cgcaaacgtc	60
cataactgaa	agtagctaag	gcaccccagc	cggaggaagt	gagctctcct	ggggcgtggg	120
tgttcgtgat	ccttgcatct	gttacttagg	gtcaaggctt	gggtcttgcc	ccgcagaccc	180
ttgggacgac	ccggccccag	cgcagctatg	aacctggagc	gagt		224

<210> 271

<211> 447

<212> DNA

<213> Homo sapiens

<400> 271

gaattcggca	cgaggctggg	ccggggcccga	gcggatcgcg	ggctcgggct	gcgggggctcc	60
ggctgcgggc	gctggggccgc	gaggcgcgga	gcttggggagc	ggagcccagg	ccgtgccgcg	120
cggcgccatg	aagggcaagg	aggagaagga	gggcggcgca	cggctggggcg	ctggcgggcg	180
aagccccgag	aagagcccga	gcgcgcagga	gctcaaggag	cagggcaatc	gtctgttcgt	240
gggccgaaag	taccgaggag	cggcggcctg	ctacggccgc	gcgatcacc	ggaaccgct	300
ggtggccgtg	tattacacca	accgggcctt	gtgctacctg	aagatgcagc	agcacgagca	360
ggccctggcc	gactgccggc	gcgccttgga	gctggacggg	cagtctgtga	aggcgcactt	420
cttcctgggg	cagtgccagc	tggagat				447

<210> 272

<211> 606

<212> DNA

<213> Homo sapiens

<400> 272

gcaactactt	atattccttt	gatggataat	gctgactcaa	gtcctgtggg	agataagaga	60
gaggttattg	atttgcttaa	acctgaccaa	gtagaaggga	tccagaaatc	tgggactaaa	120
aaactgaaga	ccgaaactga	caaagaaaat	gctgaagtga	agtttaaaga	ttttcttctg	180
tccttgaaga	ctatgatgtt	ttctgaagat	gaggctcttt	gtgttgtaga	cttgctaaag	240

gagaagtctg gtgtaataca agatgcttta aagaagtcaa gtaagggaga attgactacg 300
 cttatacatc agcttcaaga aaaggacaag ttactcgctg ctgtgaagga agatgctgct 360
 gctacaaagg atcgggtgtaa gcagttaacc caggaaatga tgacagagaa agaaagaagc 420
 aatgtggtta taacaaggat gaaagatcga attggaacat tagaaaagga acataatgta 480
 tttcaaaaca aaatacatgt cagttatcaa gagactcaac agatgcagat gaagtttcag 540
 caagttcgtg agcagatgga ggcagagata gctcacttga agcaggaaaa tgggtatact 600
 ggagaa 606

<210> 273
 <211> 598
 <212> DNA
 <213> Homo sapiens

<400> 273
 gaattcggca ccaggcccgg tcccgcggtc gcagctccag ccgcctcctc cgcgcagccg 60
 ccgcctcagc tgctcgctct gtgggtcggc cctctccggc acttgggctc cagtcgcgcc 120
 ctccaagccc ttcaggccgc cccagtgtcc tctccttct ccggccagac ccagccccgc 180
 gaagatggtg gaccgcgagc aactggtgca gaaagcccgg ctggccgagc aggcggagcg 240
 ctacgacgac atggccgcgg ccatgaagaa cgtgacagag ctgaatgagc cactgtcgaa 300
 tgaggaacga aaccttctgt ctgtggccta caagaacgtt gtggggggcac gccgctcttc 360
 ctggagggtc atcagtagca ttgagcagaa gacatctgca gacggcaatg agaagaagat 420
 tgagatggtc cgtgcgtacc gggagaagat agagaaggag ttggaggctg tgtgccagga 480
 tgtgctgagc ctgctggata actacctgat caagaattgc agcgagacc agtacgagag 540
 caaagtgttc tacctgaaga tgaaagggga ctactaccgc tacctggctg aagtggcc 598

<210> 274
 <211> 536
 <212> DNA
 <213> Homo sapiens

<400> 274
 gcaccaagag actaaacaag aaagtggatc agggagaag aaagcttcat caaagaaaca 60
 aaagacagaa aatgtcttcg tagatgaacc ccttattcat gcaactactt atattccttt 120
 gatggataat gctgactcaa gtcctgtggt agataagaga gaggttattg atttgcttaa 180
 acctgaccaa gtagaaggga tccagaaatc tgggactaaa aaactgaaga ccgaaactga 240
 caaagaaaat gctgaagtga agtttaaaaga ttttcttctg tccttgaaga ctatgatgtt 300
 ttctgaagat gaggtctctt gtgtttaga cttgctaaag gagaagtctg gtgtaataca 360
 agatgcttta aagaagtcaa gtaagggaga attgactacg cttatacatc agcttcaaga 420
 aaaggacaag ttactcgctg ctgtgaagga agatgctgct gctacaaagg atcgggtgtaa 480
 gcagttaacc caggaaatga tgacagagaa agaaagaagc aatgtggtta taacaa 536

<210> 275
 <211> 494
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (379)
 <223> n=A,T,C or G

<400> 275
 gaattcggca ccagggtcgc ggttcttgtt tgtggatcgc tgtgatcgtc acttgacaat 60
 gcagatcttc gtgaagactc tgactggtaa gaccatcacc ctcgaggttg agcccagtga 120

caccatcgag aatgtcaagg caaagatcca agataaggaa ggcattccctc ctgaccagca 180
 gaggctgac tttgctggaa aacagctgga agatggggcg accctgtctg actacaacat 240
 ccagaaagag tccaccctgc acctgggtgct ccgtctcaga ggtgggatgc aaatcttcgt 300
 gaagacactc actggcaaga ccatcaccct tgaggtggag ccagtgaca ccatcgagaa 360
 cgtcaaagca aagatccang acaaggaagg cattcctcct gaccagcaga ggttgatctt 420
 tgccggaaag cagctggaag atgggcgac cctgtctgac tacaacatcc agaaagagtc 480
 taccctgcac ctgg 494

<210> 276

<211> 484

<212> DNA

<213> Homo sapiens

<400> 276

ggcttttaac cagaagtcaa acctgttcag acagaaggca gtcacagcag aaaaatcttc 60
 agacaaaagg cagtcacagg tgtgcaggga gtgtggggcg ggcttttagca ggaagtcaca 120
 gctcatcata caccagagga cacacacagg agaaaagcct tatgtctgcg gagagtgtgg 180
 gcgaggcttt atagttgagt cagtcctccg caaccacctg agtacacact ccggggagaa 240
 accttatgtg tgcagccatt gtggggcgagg ctttagctgc aagccatacc tcatcagaca 300
 tcagaggaca cacacaaggg agaaatcggt tatgtgcaca gtgtgtgggc gaggctttcg 360
 tgaaaagtca gagctcatta agcaccagag aattcacacg ggggataagc cttatgtgtg 420
 cagagattga ggccgaggct ttgtaaagga gatcatgtct caacacacac cagaggatta 480
 catt 484

<210> 277

<211> 513

<212> DNA

<213> Homo sapiens

<400> 277

gcttgaggct gccaatcaga gcttggcaga gctgagagat cagcggcagg gggagcgcct 60
 ggaacatgca gcagctttgc gggccctaca agatcaggta tccatccaga gtgcagatgc 120
 acaggaacaa gtggaagggc ttttggctga gaacaatgcc ttgaggacta gcctggctgc 180
 cctggagcag atccaaacag caaagaccca agaactgaat atgctccggg aacagaccac 240
 tgggctggca gctgagttgc agcagcagca ggctgagtag gaggacctta tgggacagaa 300
 agatgacctc aactcccagc tccaggagtc attacgggcc aatagtcgac tgctggaaca 360
 acttcaagaa atagggcagg agaaggagca gttgacccag gaattacagg aggctcggaa 420
 gagtgcggag aagcgggaag ccatgcttgg atgagctagc aatggaaacg ctgcaagaga 480
 agtcccacac aaggaagagc ttgggagcag ttc 513

<210> 278

<211> 471

<212> DNA

<213> Homo sapiens

<400> 278

gaattcggca ccagccaagg ccctgtccct ggctcggggc cttgaagagg ccttggaagc 60
 caaagaggaa ctcgagcggg ccaacaaaat gctcaaagcc gaaatggaag acctgggtcag 120
 ctccaaggat gacgtgggca agaactcca tgagctggag aagtccaagc gggccctgga 180
 gacctagatg gaggagatga agacgcagct ggaagagctg gaggacgagc tgcaagccac 240
 ggaggacgcc aaactgcggc tggaagtcaa catgcaggcg ctcaagggcc agttcgaaag 300
 ggatctccaa gcccgggacg agcagaatga ggagaagagg aggcaactgc agagacagct 360
 tcacgagtat gagacggaac tggaagacga gcgaaagcaa cgtgccctgg cagctgcagc 420
 aaagaagaag ctggaagggg acctgaaaga cctggagctt caggccgact t 471

<210> 279
 <211> 497
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (457)
 <223> n=A,T,C or G
 <221> misc_feature
 <222> (471)
 <223> n=A,T,C or G

<400> 279
 gaattcggca cgaggccaca gaggcggcgg agagatggcc ttcagcgggtt cccaggctcc 60
 ctacctgagt ccagctgtcc ccttttctgg gactattcaa ggaggtctcc aggacggact 120
 tcagatcact gtcaatggga ccgttctcag ctccagtggga accaggtttg ctgtgaactt 180
 tcagactggc ttcagtggaa atgacattgc cttccacttc aaccctcggg ttgaagatgg 240
 agggtagctg gtgtgcaaca cgaggcagaa cggaagctgg gggcccagg agaggaagac 300
 acacatgcct ttccagaagg ggatgccctt tgacctctgc ttctgtgtgc agagctcaga 360
 tttcaagggtg atggtgaacg ggatcctctt cgtgcagtac ttccaccgcg tgcccttcca 420
 ccgtgtggac accatctccg tcaatggctc tgtgcanctg tcctacatca ncttccagac 480
 ccagacagtc atccaca 497

<210> 280
 <211> 544
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (451)
 <223> n=A,T,C or G

<400> 280
 gaattcggca ccagaatagg aacagctccg gtctacagct cccagcgtga ggcacgcaga 60
 agacgggtga tttctgcatt tccatctgag gtaccgggtt catctcacta gggagtgcc 120
 gacagtgggc gcaggccagt gtgtgtgcgc accgtgcgcg agccgaagca gggcgaggca 180
 ttgcctcacc tgggaagcac aaggggtcag ggagttccct ttccgagtca aagaaagggg 240
 tgacggacgc acctggaaaa tcgggtcact cccacccgaa tattgtgctt ttcagaccgg 300
 cttaagaaac ggcgcaccac gagactatat cccacacctg gctcagaggg tcctacgccc 360
 acggaatctc gctgattgct agcacagcag tcttagatca aactgcaagg ggggcaacga 420
 ggctggggga ggggcgcccg ccattgccc ngcttgctta ggtaaacaaa gcagccggga 480
 agcttgaact gggtagagcc caccacagct caaggaggcc tgccctgcctc tgtagctcca 540
 cctc 544

<210> 281
 <211> 527
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature

<222> (456)

<223> n=A,T,C or G

<400> 281

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gaattcggca cgaggcctcg ctcagctcca acatggcaaa aatctccagc cctacagaga 60
ctgagcgggtg catcgagtc ctcgattgctg tcttccagaa gtatgctgga aaggatgggtt 120
ataactacac tctctccaag acagagttcc taagcttcat gaatacagaa ctagctgcct 180
tcacaaagaa ccagaaggac cctgggtgtcc ttgaccgcat gatgaagaaa ctggacacca 240
acagtgatgg tcagctagat ttctcagaat ttcttaatat gattgggtggc ctagctatgg 300
cttgccatga ctcttctcctc aaggctgtcc cttcccagaa gcggacctga ggacccttg 360
gccctggcct tcaaaccac cccctttcct tccagccttt ctgtcatcat ctccacagcc 420
caccatccc ctgagcacac taaccacctc atgcanggcc cccctgccaa tagtaataaa 480
gcaatgtcct tttttaaaac atgaaaaaaa aaaaaaaaaa actcgag 527
```

<210> 282

<211> 514

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (494)

<223> n=A,T,C or G

<400> 282

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ggaagactgg agccttttgcg gcggcgctgc ccctcccctg gtccccgcga gctcggaggg 60
cccggctggt gctgcggggg ccccgaggag ttgaaaacta agcatgggga agagctgcaa 120
ggtggctcgtg tgtggccagg cgtctgtggg caaaacttca atcctggagc agcttctgta 180
tggaaccat gtagtgggtt cggagatgat cgagacgcag gaggacatct acgtgggctc 240
cattgagaca gaccgggggg tgcgagagca ggtgcgtttc tatgacacce gggggctccg 300
agatggggcc gaactgcccc gacactgctt ctcttgcaact gatggctacg tcctgggtcta 360
tagcacagat agcagagagt cttttcagcg tgtggagctg ctcaagaagg agattgacaa 420
atccaaggac aagaaggagg tcaccatcgt ggtccttggc aacaagtgtg acttacagga 480
gcagcggcgt gtanacccaa atgtggctca acac 514
```

<210> 283

<211> 484

<212> DNA

<213> Homo sapiens

<400> 283

```
gggcgggcgg tggacagtca tggcggcccc gcgcgggggt ctcatagtgc tggagggcgt 60
ggaccgcgcc gggaagagca cgcagagccg caagctgggt gaagcgtgt gcgccgcggg 120
ccaccgcgcc gaactgctcc ggttcccgga aagatcaact gaaatcggca aacttctgag 180
ttcctacttg caaaagaaaa gtgacgtgga ggatcactcg gtgcacctgc ttttttctgc 240
aaatcgctgg gaacaagtgc cgttaattaa ggaaaagttg agccagggcg tgaccctcgt 300
cgtggacaga tacgcatttt ctgggtgtgg cttcaccggt gccaaaggaga atttttccct 360
agactgggtg aaacagccag acgtgggcct tcccaaacc gacctgggtc tgttctcca 420
gttacagctg gcggatgctg ccaagcgggg agcgtttggc catgagcgt atgagaacgg 480
ggct 484
```

<210> 284

<211> 514

<212> DNA

<400> 284

<210> 285

<211> 383

<212> DNA

<400> 285

gaattcggca	cgaggccggg	ctccaccgcg	catectgctc	cactctggcg	accgcccccg	60
gggcccccg	cgcgggcgcg	ggcgccgcca	tgggcgagga	ggactactat	ctggagctgt	120
gcgagcggcc	ggtgcagttc	gagaaggcga	accctgtcaa	ctgcgtcttc	ttcgatgagg	180
ccaacaagca	ggttttttgc	gttcgatctg	gtggagctac	tggcgtggta	gttaaaggcc	240
cagatgatag	gaatcccatc	tcatttagaa	tggatgacaa	aggagaagtg	aagtgcatta	300
agtttttcct	agaaaataag	atattggctg	ttcagaggac	ctcaaagact	gtggattttt	360
gtaattttat	ccctgataat	tcc				383

<210> 286

<211> 943

<212> DNA

<400> 286

gaattcggca	ccagggccgt	ggcggaggag	gagcgtgca	cggtggaagc	tggggccgac	60
ctcacctacg	cggagttcgt	gcagcagtac	gtgcgccccct	gatcgcgga	gtcgcgtcct	120
gttcaccggc	ccgtctgcc	cgaccgccca	aggccgcctt	cccctgacct	cgcgcgcacg	180
cgtggggctg	gggcggcgag	gctggcggtc	cggcctggcc	gcgactctgc	ccttctttcc	240
agaggttcg	ggccctgtgc	tcccgcgaca	ggttgctggc	ttcgtttggg	gacagagtgg	300
tccggctgag	caccgccaac	acctactcct	accacaaagt	ggacttgccc	ttccaggagt	360
atgtggagca	gctgctgcac	ccccaggacc	ccacctccct	gggcaatgg	gaggcagccc	420
taggcggcgg	taggggggtg	ggacgcttgg	agtctccagg	tgccaggatc	cctgtccccg	480
ccgtctctgt	tggcagacac	cctgtacttc	ttcggggaca	acaacttcac	cgagtgggcc	540
tctctctttc	ggcactactc	cccaccccca	tttggcctgc	tgggaaccgc	tccagcttac	600
agcttttgaa	tgcaggagc	tggctcgggg	gtgcccttcc	actggcatgg	accggggtac	660
tcagaagtga	tctacggtcg	taagcgtctg	ttcctttacc	cacctgagaa	gacgccagag	720
ttccacccca	acaagaccac	actggcctgg	ctccgggaca	catacccagc	cctgccaccg	780
tctgcacggc	ccctggagtg	taccatccgg	gctggtgagg	tgtgtactt	ccccgaccgc	840
tggtggcatg	ctacgctcaa	ccttgacacc	agcgtcttca	tctccacctt	cctcggctag	900
ccaaaacagc	tggcaggact	gccggtcaca	caccagcacg	tcc		943

<210> 287

<211> 1143

<212> DNA

<213> Homo sapiens

<400> 287

```

gaattcggca cgaggggaaga acagctgttg gaacaacaag aatatattaga aaaagaaatg 60
gaggaagcaa agaaaatgat atcaggacta caggccttac tgctcaatgg atccttacct 120
gaagatgaac aggagaggcc cttggccctc tgtgaaccag gtgtcaatcc cgaggaacaa 180
ctgattataa tccaaagtcg tctggatcag agtatggagg agaatacagga cttaaagaag 240
gaactgctga aatgtaaaca agaagccaga aacttacagg ggataaagga tgccttgacg 300
cagagattga ctcagcagga cacatctgtt cttcagctca aacaagagct actgagggca 360
aatatggaca aagatgagct gcacaaccag aatgtggatc tgcagaggaa gctagatgag 420
aggaaccggc tcttgggaga atataaaaaa gagctggggc agaaggatcg ccttcttcag 480
cagcaccagg ccaagttaga agaagcactc cggaaactct ctgatgtcag ttaccaccag 540
gtggatctag agcgagagct agaacacaaa gatgtcctct tggctcactg tatgaaaaga 600
gaggcagatg aggcgaccaa ctacaacagt cacaactctc aaagcaatgg ttttctcctt 660
ccaacggcag gaaaaggagc tacttcagtc agcaacagag ggaccagcga cctgcagctt 720
gttcgagatg ctctccgcag cctgcgcaac agcttcagtg gccacgatcc tcagcaccac 780
actattgaca gcttggagca gggcatttct agcctcatgg agcgccctgca tgttatggag 840
acgcagaaga aacaagaaag aaagggttcgg gtcaagtcac ccagaactca agtaggtagt 900
gaataccggg agtcttggcc ccctaactca aagttgcctc actcacagag ctctccaact 960
gtcagcagca cctgtactaa agtgctctat ttcactgacc ggtcacttac gcccttcatg 1020
gtcaatatac caaagagggt ggaggagggt acgttaaagg attttaaagc agctattgat 1080
cggaaggaa atcaccggta tcacttcaaa gcactggatc ctgagtttgg cactgtcaaa 1140
gag 1143

```

<210> 288

<211> 881

<212> DNA

<213> Homo sapiens

<400> 288

```

gtgagagcgg gccgaggaga ttggcgacgg tgtcgcccggt gttttcgttg gcgggtgcct 60
gggctgggtg gaacagccgc ccgaaggaa caccatgatt tcggccgcgc agttgttgga 120
tgagttaatg ggccgggacc gaaacctagc cccggacgag aagcgacgca acgtgcggtg 180
ggaccacgag agcgtttgta aatattatct ctgtggtttt tgcctgcgg aattgttcac 240
aaatacacgt tctgatcttg gtccgtgtga aaaaattcat gatgaaaatc tacgaaaaca 300
gtatgagaag agctctcggt tcatgaaagt tggctatgag agagattttt tgcgatactt 360
acagagctta cttgcagaag tagaacgtag gatcagacga ggccatgctc gtttggcatt 420
atctcaaaac cagcagtcct ctggggccgc tggcccaaca ggcaaaaatg aagaaaaaat 480
tcaggttcta acagacaaaa ttgatgtact tctgcaacag attgaagaat tagggtctga 540
aggaaaagta gaagaagccc aggggatgat gaaattagtt gagcaattaa agaagagag 600
agaactgcta aggtccacaa cgtcgacaat tgaaagcttt gctgcacaag aaaaacaaat 660
ggaagtttgt gaagtatgtg gagccttttt aatagtagga gatgccagc cccgggtaga 720
tgaccatttg atgggaaaac aacacatggg ctatgccaaa attaaagcta ctgtagaaga 780
attaaaagaa aagttaagga aaagaaccga agaacctgat cgtgatgagc gtctaaaaaa 840
ggagaagcaa gaaagagaaa aaaaaaaaaa aaaaactcga g 881

```

<210> 289

<211> 987

<212> DNA

<213> Homo sapiens

<400> 289

```

gaattcggca cgaggggactg tggtttccag gaatggtggc gtctcacgct tcttgtgctt 60
tttcccttgg ggcctccgag cggctggggg tgggggactg ggcaggaggc tccctgtaaa 120
catttggact tgggctgggg caggggctgg tgttgggcaa agctgggggt ccaggctgga 180

```

```

gaagcagggg cccctccaga cgcagccttg ggagactcag catgtgcccc cctccccctca 240
tcacagaaca agacaatggt taaaaaaccag aacagatgcc cagaaggggg taccatggcc 300
attaccagca tctcagacaa gggcaggctt caaacaggga ggctgtggc aacccctccc 360
ctacgtcttg agctgagggg acaggggggag ctgagaacaa agagaggaaa gaggagaaaa 420
gcggcggggg aacaggcggg ggcgtgatc ttcttgcccc catcttcctc aggggttggg 480
gggtacaaag tcggcgggtg cccatccccg caggccccgc tgccccctag aagaggccgc 540
agtccttcag gttgttcttg atgatgacat cggtgacggc gtcaaacacg aactgcacgt 600
tcttggtgtc ggtggcgcac gtgaagtgcg tgtagatctc cttggtgtct ttgcgcttat 660
tcaggctctc aaacttactc tggatgtagc tggctgcctc atcataattg ttggccccctg 720
tatactcagg gaagcagatg gtcaggggac tgtgtgtgat cttctcctca aacaggctct 780
tcttggtgag gaagaggatg atggacgtgt ctgtgaacca cttgttggtg cagatgctat 840
cgaatagctt catgctctca tgcattgcgt tcctctctc gtcctcagct agcaccaagt 900
cataggcgct caaggctacg cagaagatga tggctgtgac gccctcaaag cagtggatcc 960
acttcttccg ctcagaccgc tgaccac 987

```

```

<210> 290
<211> 300
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

```

```

<400> 290
gattcaagat gtacccatt gactttgaga aggatgatga cagcaacttt catatggatt 60
tcattcgtggc tgcattcaac ctccgggcag aaaactatga cattccttct gcagaccggc 120
acaagagcaa gctgattgca gggaagatca tccagccat tgccacgacc acagcagccg 180
tgggtggcct tgtgtgtctg gagctgtaca aggttgtgca ggggcaccga cancttgact 240
cctacangaa tgggtgcctc aacttgagcc ctgcctttct ttggtttctc tgaaccctt 300

```

```

<210> 291
<211> 352
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(352)
<223> n = A,T,C or G

```

```

<400> 291
aaccaagctg ccaccggggg tggatcggat gcggcttgag aggcattctgt ctgccgagga 60
cttctcaagg gtatttgcca tgtccctga agagtgtggc aagctggctc tgtggaagcg 120
gaatgagctc aagaagaagg cctctctctt ctgatggccc ccacctgctc cgggacggcc 180
cccttaccce tgctgcttca gggtttttcc ccggcggggt gggaggggca ggaggtgggg 240
tggaatngg gtgggncct ttctcaggt agagnngggg gccaaaacct ctgcngtccc 300
cggagngagc tatggacttt cttccccctc acaaggntgg gggcctcctg ct 352

```

```

<210> 292
<211> 511
<212> DNA

```

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(511)

<223> n = A,T,C or G

<400> 292

cgcggtggct	gcgcactcng	cctgagaaac	tgggcaagcg	cgcagtgtcg	actccccggt	60
ctatgccagg	cgcatctcag	ctaattccaa	agtaaatgag	aaacttagaa	aaagattgcc	120
aattccaaat	caacatattt	agagaaaatt	ggaaaaggag	aagcttacta	cagctttatt	180
tgaggacttt	ttaaagaacg	ctgggttcta	tctgtgagct	gcaaattctg	gagcaaaaac	240
cagagacatt	gccagagcaa	acaagaacag	aaatacaaat	ggagaactgg	tcaaaagaca	300
taacccacag	ttatcttgaa	caagaaacta	cggggataaa	taaaagtacg	canccagatg	360
agcaactgac	tatgaattct	gagaaaagta	tgcatcggaa	atccactgaa	ttagnaatg	420
aaataacatg	ngagaacaca	gaatggccag	gggcagagat	caacgaattt	tcanatcatc	480
agttcttata	cagatgatga	gtctgtttac	t			511

<210> 293

<211> 526

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(526)

<223> n = A,T,C or G

<400> 293

gataaaaaga	actttaatgg	aaggcactgt	tgtccaaaat	cacataaagg	gtaagagccc	60
acacgggtacc	accctgctct	cctacttctc	aaaccacat	ccaccacca	gacaggaggg	120
tgcanacccc	acaggaaatt	acctcccgga	gcactgactg	atatttttcc	ttaaaacaaa	180
aaaatggctg	tctcagacta	ataacagaac	atcttaagag	ctataccagc	tattacagcc	240
tggtaatana	agcagctttc	taanaattcc	caagtattata	anaggcccaa	naaatgcatt	300
tattctgttg	tctattaagc	ctccatgaca	aggagaaagt	tatgagtaaa	tccttggttc	360
atcaggagtt	aagagctgtg	ngcctcatga	ggagttaana	gctgtgtgca	taagcagggt	420
caagaaacaa	actcctgttt	gtttgcctct	ttgatgggtc	aaaaacattc	agctgctttc	480
acctctanga	caaatgctt	aaagaattta	ctctcatcac	cttggg		526

<210> 294

<211> 601

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(601)

<223> n = A,T,C or G

<400> 294

actttaaaag	ccaaatatat	ttttaaaaga	tcatgcttat	aataagtaaa	ttacncatta	60
aggaaacatc	aaaataaagt	agatgaataa	aaaggcacac	tcgaaaaatt	tgagcgcaga	120
aaggacagtt	ctttttgttt	tgtttcta	gtcggagaa	aaagaaagag	atatattaaa	180
atcattgttt	tcaagtgaag	gtttctgtca	gttgaagtag	ttagcaatgg	cttcttttct	240

```

cccgtgtcca aagcaggctc ttcttgcgct gacttctgag gagnggttca gtcctctgcc 300
atgtataggc gatacatcaa ggcgacggcc actgcagaga tggcagggat caccagttg 360
gtccaccaac tggaactaga atcaatagta gtgataagag tttccggagg cttgtttaac 420
tttgggtctgt catctggatg gagctcccca atgatgaatg ttttggacat ttccctggca 480
tctgtagant gcccgacatc ctcaaagttc tcagtagcng tcacctccac ttgttccctt 540
aaaacttctt ccccaccagg atgctcttcc agaaatttgg gncaaategn acaccttgtg 600
g 601

```

```

<210> 295
<211> 262
<212> DNA
<213> Homo sapien

```

```

<400> 295
cccttagccc caagggccct gggggcagcc accctcccgc ctgtcggccc gtagatttat 60
caaggggtgtt atgggcccag ctttgggggg ccagtcccga tgcactttga ggggtgttgg 120
agaggggact ccccccactcg cacttaactc aacggctctc gggccctggg gctgttttta 180
ccatgtttgt ttttgaagct caggtgtctc acgtctgggc tgcaccaggc gaagagagaa 240
attaaagatt tgaggttttt cc 262

```

```

<210> 296
<211> 598
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(598)
<223> n = A,T,C or G

```

```

<400> 296
gttagaaciaa ctcagcaaaa taaaattcct gtttattgtt ggacaacatt gtttcacaca 60
tacatcaaac aggccaaaaa aaataaacag caacttcata gacaaaaaag gaaaaaaaaa 120
gaaacctttt atcttttgcc tttttaacca tctcatacaa accaactact tatagtacag 180
ctaagtacat acacaaaaaa gttactggaa tgctcggaat aagattgttt ttctgttgtc 240
atttttgctt tttttacaag gntttttttc tcctttgaga ttataatgaa catggnacac 300
ccacaagtaa agtcagaagt aggacagana acgctccgaa ggctggtttg gtcacccgan 360
atcattaaaa atggctgacc ctaacaatat gtacaaaaat ataaaatgta aataaaaaat 420
acaaacaaat ttccttttta aagtactttt aagaaaaaaa gcagggcctt ggaagttttg 480
gttctttttt cctcccctgt tgcaaattct catggtttgg gttgggtggn gganancccg 540
tgtcatctgc ggggtggcact gccccggngg gcggggcgggc ctctctctcg aangngac 598

```

```

<210> 297
<211> 509
<212> DNA
<213> Homo sapien

```

```

<400> 297
agaacacagg tgtcgtgaaa actacccta aaagccaaaa tgggaaagga aaagactcat 60
atcaacattg tcgtcattgg acacgtagat tcgggcaagt ccaccactac tggccatctg 120
atctataaat gcggtggcat cgacaaaaga accattgaaa aatttgagaa ggaggctgct 180
gagatgggaa agggctcctt caagtatgcc tgggtcttgg ataaactgaa agctgagcgt 240
gaacgtggta tcaccattga tatctccttg tggaaatttg agaccagcaa gtactatgtg 300
actatcattg atgccccagg acacagagac tttatcaaaa acatgattac agggacatct 360

```

```

caggctgact gtgctgtcct gattgttgct gctgggtgtg gtgaatttga agctgggtatc 420
tccaagaatg ggcaggaccc gagagcatgc ctttctggct tacacactgg gtgtgaaaca 480
actaattgtc ggtgttaaca aaatggatt 509

```

```

<210> 298
<211> 267
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(267)
<223> n = A,T,C or G

```

```

<400> 298
gggacggggg aaaggagacg cttcttctc ttgctgctct tctcgttccc gagatcagcg 60
gcggcggtga ccgcgagtgg gtcggcaccc tctccggctc cgggngcnaa caatgctgac 120
tgatagcgga ggcggnggca cctccttnna ggaggacctg gactctgtgg ctccgcgac 180
cgccccagct ggggcctcgg agccgcctcc gccgggaggg gtcgggtctgg ggatccncac 240
cgngaggctn tttggggagg gcggggcc 267

```

```

<210> 299
<211> 121
<212> DNA
<213> Homo sapien

```

```

<400> 299
ggcacgaggg ccctcggagc tcgtttccag atcgaggtaa gagggacttt cttaaaggcc 60
tagtctatgg gatggggcgg cggaggggaat tttttgagaa ataaaatgaa gctgcagtgt 120
a 121

```

```

<210> 300
<211> 533
<212> DNA
<213> Homo sapien

```

```

<400> 300
aaggtgcaca gtatttgatg caggctgctg gtcttggtcg tatgaagcca aacacacttg 60
tccttggtatt taagaaagat tggttgcaag cagatatgag ggatgtggat atgtatataa 120
acttatttca tgatgctttt gacatacaat atggagtagt gggtattcgc ctaaaagaag 180
gtctggatat atctcatctt caaggacaag aagaattatt gtcatcaca gagaaatctc 240
ctggcaccaa ggatgtggta gtaagtgtgg aatatagtaa aaagtccgat ttagatactt 300
ccaaaccact cagtgaaaaa ccaattacac acaaagttga ggaagaggat ggcaagactg 360
caactcaacc actgttgaaa aaagaatcca aaggccctat tgtgccttta aatgtagctg 420
acaaaaagct tcttgaagct agtacacagt ttcagaaaaa acaaggaaag aatactattg 480
atgtctggtg gctttttgat gatggagggt tgaccttatt gataccttac ctt 533

```

```

<210> 301
<211> 560
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature

```

<222> (1)...(560)
 <223> n = A,T,C or G

<400> 301
 ataaatgata cctttttattg taagtaaatgc gcaacactgg cctggccttg cactgcaagc 60
 cctcgggtcaa gatatagtca aataactatg gctgcagggt ccacagttcc acaataacca 120
 tggctgcacg atccacaatt cagacacaga catagagctg ggggtgggtgg aaggggcagg 180
 aggggtggcag agtgcggact gtccccagcc ctggcctctc catgcanagt tggcccaggc 240
 agacacaccc catggaatga tgagaaagtg acggcacggc cccttccac agcaagcctg 300
 gggctgccag gaactgccct tcanaacctt tgggcccagg tcnccctgaa nccccacaac 360
 tttttatctg gaataagtat taaaaaacia taaattaagc aaacaacntg gnccttgaag 420
 gatgttgacc nacatgggtc acagtttttg gcncaaaaaa ataagggtctg gtttgctttt 480
 tttggaaggc agggtttgtg gnttggcttt caaatnattt tcaaaccatt ccccaggag 540
 gganaacccc cgggggggaa 560

<210> 302
 <211> 599
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(599)
 <223> n = A,T,C or G

<400> 302
 gcaaagttac aaattttattg gtctggaaat aaatacaaat atctcattaa naaactcctc 60
 tggaaagact tgtgcacaat agtttcccat ccgtactcag cctctcttgc cccgatcccc 120
 gacttttcta ctcaaggcca gggaaggcct ccaaggngat gggcggcagg taacgagtca 180
 ttgcctctca cgccacctgg aaggctggac tacttcctcc tcccaactgc ggggtccan 240
 aaatcctcgg gtcccagngg ctgacttaca atattcaatt cactctgacc aaacttccta 300
 tganaaaatc cacgngagc caaaatgaaa agtacaaggc agtagtacag gaacctggca 360
 gccgactgg ccgccanana acgtcagtgg ngctgccccca ttcggcgaaa ggtagggag 420
 caggaaaaga ggaagcagga gaggaagga aagtcctatg gaatatgtat tccanaatcc 480
 ttacattttc tcagccaccg ctccccacgt gagttccac cccacccccg acaagaagca 540
 aagagttctg aggatccaag aacgtgaccg ggtcanacan gttcagctac tgagttcac 599

<210> 303
 <211> 591
 <212> DNA
 <213> Homo sapien

<400> 303
 cggagttgta acgtccact gactgataga gcgaccggcc gaccatggcg cccggagtgg 60
 cccgcgggcc gacgccgtac tggagggttg gcctcgggtg cgccgcgctg ctctgctgc 120
 tcatcccggg ggccgccgag caggagcctc ccggagctgc ttgttctcag aacacaaaca 180
 aaacctgtga agagtgcctg aagaacgtct cctgtctttg gtgcaacact aacaaggctt 240
 gtctggacta cccagttaca agcgtcttgc caccggcttc cctttgtaaa ttgagctctg 300
 cacgctgggg agtttggttg gtgaactttg aggcgctgat catcaccatg tcggtagtcg 360
 ggggaaccct cctcctgggc attgccatct gctgctgctg ctgctgcagg aggaagagga 420
 gccggaagcc ggacaggagt gaggagaagg ccatgcgtga gcgggaggag aggcggatac 480
 ggcaggagga acggagagca gagatgaaga caagacatga tgaaatcaga aaaaaatatg 540
 gcctgtttta agaagaaaac ccgtatgcta gatttgaaaa caactaaagc g 591

<210> 304
 <211> 441
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(441)
 <223> n = A,T,C or G

<400> 304

gctggacgga	gacctgctgg	aggaggagga	gctggaggaa	gcagaggagg	aggaccggtc	60
gtcgtctgtg	ctgctgtcgc	cgcccgcggc	caccgcctct	cagacccagc	agatcccagg	120
cgggtccctg	gggtctgtgc	tgtgtccagc	cgccagggtc	gatgcccggg	aggcggcggc	180
ggcggcgggg	gtgctgtacg	gaggggacga	tgcccagggc	atgatggcgg	cgatgctgtc	240
ccacgcctac	ggccccggcg	gttgtggggc	ggcggcggcc	gccctgaacg	gggagcaggc	300
ggccctgctc	cggagaaaga	gcgtcaacac	caccgagtgc	gtcccgggtg	ccagctccga	360
gcacgtcgcc	gagatcgtcg	gccgccaggg	ttgtaaaatt	aaagcactga	nagccaagac	420
aaacacgtat	atcaagactc	c				441

<210> 305
 <211> 491
 <212> DNA
 <213> Homo sapien

<400> 305

tcgccatgcc	cccttcttag	cactgcaccg	ccagggtccat	gctgctgcca	ccccagacct	60
gggctttgcc	tgccacctct	gtgggcagag	cttccgaggc	tgggtggccc	tggttctgca	120
tctgcgggcc	cattcagctg	caaagcggcc	catcgcttgt	cccaaagtcg	agagacgctt	180
ctggcgacga	aagcagcttc	gagctcatct	gcggcgggtg	caccctcccg	ccccggaggc	240
ccggcccttc	atatgcggca	actgtggccg	gagctttgcc	cagtgggacc	agctagtgtg	300
ccacaagcgg	gtgcacgtag	ctgaggccct	ggaggaggcc	gcagccaagg	ctctggggcc	360
ccggcccagg	ggccgccccg	cggtgaccgc	cccccgcccc	ggtggagatg	ccgtcgaccg	420
ccccttccag	tgtgcctggt	gtggcaagcg	cttccggcac	aagcccaact	tgatcgctca	480
cccgcgcgtg	c					491

<210> 306
 <211> 547
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(547)
 <223> n = A,T,C or G

<400> 306

tctctttctt	ttaagacagg	aatgtaagcc	acaacattta	caaatacaat	gtttttaactc	60
tctacatgta	ggaagccaac	ctgctccttt	ttgatcttct	tctttggcac	aacctcagtg	120
gatttctctg	attcagaacg	agttctaatt	gatcttctct	gttgcttctt	ttctactgag	180
cctgtagaac	cagatgttgc	ttcaggagat	gatacactct	gcgttggctt	ttcattttctc	240
tggtttggtg	tagaaattat	aagcctgtct	tgccccctga	cacttatttc	tgttttgtta	300
ccaattccct	ttgttgaata	aacaaattga	tcgataaatt	tcccatcccc	tgtagcattc	360
tgaagagcaa	acacttggtc	aattttcaca	actggagaca	tgttacactt	ctgcaaatacc	420

aggctccctt tgtgcatccg taatggaagc tggtaaggat ttccttgctg ccgcagtttt 480
 ccaggctatt ttaacaggcg gnggctcttc ctctttccgc acttgtgtgc cgctctggc 540
 tatgtct 547

<210> 307
 <211> 571
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(571)
 <223> n = A,T,C or G

<400> 307

cgctgcatgt	gataatgtca	tcattttattt	ttaaattgggt	ctaaattgca	nattttaagtt	60
gatttcaa	caaccctatt	tttaaattac	ttttaatagg	aanaaatgaa	gcaaggacat	120
acataatcta	ctatatattga	aggactcaaa	caaatacatg	tttggctgtg	aattctgtac	180
tctcaccaaa	acagagataa	aaatccacct	aaaatacact	ttccttcatt	tagtgcttgt	240
ggganaaggt	caagtattgc	actttaaaat	tactttcatc	taacatttgc	cccaactttc	300
cccctgaatt	cactatatgt	tttcagcaaa	catgatttta	taaattttaa	gtataaaaagc	360
aactaggttt	tctaattcaa	ctttggaagg	tttactttac	tctacanagc	tattttttgta	420
aaacggcata	tttacttaca	aaattganag	ataggggcat	ccagctgagg	tacatttcct	480
cccttggcgt	tgagtttctg	gacttgggtc	gggggcacag	gcttgtgtga	ctgccccgtg	540
gcccataca	tggcctggac	cccaggatgc	g			571

<210> 308
 <211> 591
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(591)
 <223> n = A,T,C or G

<400> 308

ctccttatgt	gtctgcctac	ttcattcttc	ggcatttcct	gcttatccaa	gttcaccatt	60
tcaggtcacc	actggatata	agttgcctgt	atataattat	caggcatttc	ctgcttatcc	120
aagttcacca	tttcagggtca	ccactggata	tcagttgcct	gtatataatt	atcaggcatt	180
tcctgcttat	ccaagttcac	catttcagggt	caccactgga	tatcagttgc	ctgtatataa	240
ttatcaggca	tttcctgctt	atccaagtgc	accatttcag	gtcaccactg	gatatcagtt	300
gcctgtatat	aattatcagg	catttcctgc	ttatccaagt	tcaccatttc	aggtcaccac	360
tggatatcag	ttgcctgtat	ataattatca	ggcatttcct	gcttatccaa	gttcaccatt	420
tcaggtcacc	actggatata	agttgcctgt	atataattat	caggcatttc	ctgcttatcc	480
aaattcagca	gttcagggtca	ccactggata	tcagttccat	gtatacaatt	accagatgcc	540
accgcagtgc	cctgttgggg	gagcaaagga	gaaatntgtg	gaccgaagca	t	591

<210> 309
 <211> 591
 <212> DNA
 <213> Homo sapien

<400> 309

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<210> 310
<211> 488
<212> DNA
<213> Homo sapien
```

```
<210> 311
<211> 511
<212> DNA
<213> Homo sapien
```

```
<220>  
<221> misc_feature  
<222> (1)...(511)  
<223> n = A,T,C or G
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<210> 312
<211> 591
<212> DNA
<213> Homo sapien
```

```
<210> 313
<211> 373
<212> DNA
<213> Homo sapien
```

<400> 313

```
<210> 314
<211> 591
<212> DNA
<213> Homo sapien
```

<400> 314

$\langle 210 \rangle$	315
$\langle 211 \rangle$	591

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 315

aagcccttca	ccaacaaaga	tgcctatact	tgtgcaaatt	gcagtgcctt	tgtccacaaa	60
ggctgccgag	aaagtctagc	ctcctgtgca	aaggtcaaaa	tgaagcagcc	caaagggagc	120
cttcaggcac	atgacacatc	atcactgccc	acggtcatta	tgagaaacaa	gccctcacag	180
ccaaggagc	gtcctcgggc	cgcagtcctc	ctgggtggatg	aaaccgctac	cacccaata	240
tttgccaata	gacgatccca	gcagagtgtc	tcgctctcca	aaagtgtctc	catacagaac	300
attactggag	ttggcaatga	tgagaacatg	tcaaacacct	ggaaattcct	gtctcattca	360
acagactcac	taaataaaaat	cagcaaggtc	aatgagtcaa	cagaatcact	tactgatgag	420
ggtacagaca	tgaatgaagg	acaactactg	ggagactttg	agattgagtc	caaacagctg	480
gaagcagagt	cttggagtcg	gataatagac	agcaagtttc	taaaacagcc	aaaagaaaga	540
tgtgggtcaa	acngcgagaa	gtaatatatg	agttggatgc	agacagagtt	t	591

<210> 316
<211> 591
<212> DNA
<213> Homo sapien

<400> 316

gtttttataa	gaataaaaatt	ccattcaagc	cagatgggtgt	ttacattgaa	gaagttctaa	60
gtaaattggaa	aggagattat	gaaaaactgg	agcacaacca	cacttacatt	caatggcttt	120
tccccctgag	agaacaaggc	ttgaacttct	atgccaaaga	actaactaca	tatgaaattg	180
aggaattcaa	aaaaacaaaa	gaagcaatta	gaagattcct	cctggcttat	aaaatgatgc	240
tagaattttt	tgggaataaaa	ctgactgata	aaactggaaa	tgttgctcgg	gctgttaact	300
ggcaggaaaag	atttcagcat	ctgaatgagt	cccagcacaa	ctattttaaga	atcactcgta	360
ttcttaaaaag	ccttgggtgag	cttggatatg	aaagttttaa	atctcctctt	gtaaaattta	420
ttcttcatga	agctcttggtg	gagaataacta	ttcccaatat	taagcagagt	gctctagagt	480
attttgttta	tacaattaga	gacagaagag	aaaggagaaa	gctcctgcgg	ttcgcccaga	540
aacactacac	gccttcagag	aactttatct	ggggacccgc	ctcgaaaaga	a	591

<210> 317
<211> 323
<212> DNA
<213> Homo sapien

<400> 317

ccaagctacg	gaagcaagtg	gaagagattt	ttaatttgaa	atttgctcaa	gctcttggac	60
tcaccgaggc	agtaaaaagta	ccatatcctg	tgtttgaatc	aaaccgggag	ttcttctatg	120
tggaaggctt	gccagagggg	attcccttcc	gaagccctac	ctgggttgga	attccacgac	180
ttgaaaggat	cgtccacggg	agtaataaaa	tcaagttcgt	tgtaaaaaaa	cctgaactag	240
ttatttccta	cttgcctcct	gggatggcta	gtaaaataaa	cactaaagct	ttgcagtccc	300
ccaaaagacc	acgaagtcct	ggg				323

<210> 318
<211> 591
<212> DNA
<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(591)
 <223> n = A,T,C or G

<400> 318
 gatggcgtagc ttggcttgga gactggcgcg gcgttcgtgt ccgagttctc tgcagggtcac 60
 tagtttcccc gtagttcagc tgcacatgaa tagaacagca atgagagcca gtcagaagga 120
 ctttgaaaat tcaatgaatc aagtgaact cttgaaaaag gatccaggaa acgaagtga 180
 gctaaaactc tacgcgctat ataagcaggc cactgaagga ccttgtaaca tgcccaaacc 240
 aggtgtattt gacttgatca acaaggccaa atgggacgca tggaatgccc ttggcagcct 300
 gcccaaggaa gctgccaggc agaactatgt ggatttggtg tccagtttga gtccttcatt 360
 ggaatcctct agtcagggtg agcctggaac agacaggaaa tcaactgggt ttgaaactct 420
 ggtggtgacc tccgaagatg gcatcacaaa gatcatgttc aaccggccca aaaagaaaaa 480
 tgccataaac actgagatgt atcatgaaat tatgcgtgca cttaaagctg ccagcaanga 540
 tgactcaatc atcacttggt ttaacaggaa atggtgacta ttacagtagn g 591

<210> 319
 <211> 591
 <212> DNA
 <213> Homo sapien

<400> 319
 gaattcggca cgaggttgct gctaagcgaa cgcccttttg agcttacgga ggccttctga 60
 aagacttcac tgctactgac ttgtctgaat ttgctgccaa ggctgccttg tctgctggca 120
 aagtctcacc tgaaacagtt gacagtgtga ttatgggcaa tgcctgcag agttcttcag 180
 atgctatata tttggcaagg catgttggtt tgcgtgtggg aatcccaaag gagacccag 240
 ctctcacgat taataggctc tgtggttctg gttttcagtc cattgtgaat ggatgtcagg 300
 aaatttgtgt taaagaagct gaagttggtt tatgtggagg aaccgaaagc atgagccaag 360
 ctccctactg tgtcagaaat gtgcgttttg gaaccaagct tggatcagat atcaagctgg 420
 aagattcttt atgggtatca ttaacagatc agcatgtcca gctcccatg gcaatgactg 480
 cagagaatct tgctgtaaaa cacaaaataa gcagagaaga atgtgacaaa tatgccctgc 540
 agtcacagca gagatggaaa gctgctaata atgctggcta ctttaatat g 591

<210> 320
 <211> 591
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(591)
 <223> n = A,T,C or G

<400> 320
 ggctccggcg tctgcagggg tcgccgagct aaccctgtgg taggcgagtg gggcggggcg 60
 gccggcacca tgcgcaggga ggccaaccgt ggcaccgaga gcaagaaaat gagctctgag 120
 ctcttcaccc tgacctatgg tgccctggtc acccagctat gtaaggacta tgaaaatgat 180
 gaagatgtga ataaacagct ggacaaaatg ggctttaaca ttggagtccg gctgattgaa 240
 gatttcttgg ctcggtcaaa tggtgggagg tgccatgact ttcgggaaac tgcggatgtc 300
 attgccaagg tggcggtcaa gatgtacttg ggcattcact caagcattac taattggagc 360
 ccagctggtg atgaattctc cctcattttg gaaaataacc ccttggtgga ctttgtggaa 420
 cttcctgata accactcatc ccttatattat tccaatctct tgtgtggggg gttgcgggga 480

gctttggaga tggccagat ggctngngga ggcccaagtt tgtccaggac accctnaaag 540
gagacgggng tgacagaaat ccggatgaga ttcacaggc ggattganga c 591

<210> 321
<211> 260
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(260)
<223> n = A,T,C or G

<400> 321
ctgcttggct ccacacgtgg gccgccgtag gtattccgac cggtaattcc tectattggt 60
gtgcagcagc cacattgaag gatagagtgg cagcagaggc caaggatcgt gagttgatgg 120
agtttgctgc tgaaaatgaa gggaagtctg ggggaggtct ccacagcgta gctgaggggg 180
tgccggctaag tccagagcct ggcagggagg gagtaaggga cttagcaggg gcggaggagt 240
tctgcggngg anaggagggg 260

<210> 322
<211> 559
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(559)
<223> n = A,T,C or G

<400> 322
ttccacatga catggagtgt gaagctggat gagcacatca ttccactggg aagcatggca 60
nttaacagca tctcaaaact gactnanctc acccagtctt ccatgtattc acttcctaat 120
gcacccactc tggcanacct gnaggacnat acacatgaag ncantgatga tcagccagan 180
aancctcact ttgactctcg canngtgata tttgagctgg attcatgcaa tggnagtggg 240
aaagtttgcc ttgtctacaa aagtgggaaa ccagnattag cagaanacac tgagatctgg 300
ttcctgnaca nancgttata ctggcatitt ctcacanaca cctttactgc ctattaccgc 360
ctgctcatca cccacctggg cctgccccag tggcaatatg ccttcccagc tatggcatta 420
gcccacaggc caagcaatgg ttcagcatgt ataaacctat cacctacaac acaaacctgc 480
tcacagaaga naccgactcc tttgtgaata agctagatcc canctnagtg ttttaagagca 540
agaacaagat cgttatccc 559

<210> 323
<211> 492
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(492)
<223> n = A,T,C or G

<400> 323
cctgtctccc agccgtacca gcgagggctc ggccggcagc gccgggctgg ggggcggcgg 60

cgccggcgcc	ggagccgggg	tgggtgcagg	cgccggcggg	ggcagcgggc	cgagcagcgg	120
cgccggggcc	ggggggctgc	aaccagcag	ccgcgctggc	ggcggccggc	cctccagccc	180
cagcccgtcg	gtggtgagcg	agaaggagaa	ggaagagttg	gagcggctgc	agaaagagga	240
ggaggagagg	aagaagaggc	tgcagctgta	tgtgttcgtg	atgcgctgca	tcgcctaccc	300
ctttaatgcc	aagcagccca	ccgacatggc	tcgccggcag	cagaagatca	gcaaacagca	360
gctgcagaca	gtcaaggacc	ggtttcaggc	tttcctcaat	ggggaaaccc	anatcatggc	420
tgacgaagcc	ttcatgaacc	gctgtngcag	agttactatg	aggtgttcct	gaagaccacc	480
cgtgtggccg	ca					492

<210> 324

<211> 474

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(474)

<223> n = A,T,C or G

<400> 324

aatttcagca	acatacttct	caattttcttc	aggattttaa	atcttgaggg	attgatctcg	60
cctcatgaca	gcaagttcaa	tgtttttgcc	acctgactga	accacttcca	ggagtgcctt	120
gatcaccagc	ttaatgggtca	natcatctgt	ttcaatggct	tcgtcagtat	agttcttctc	180
cagnaactca	cgcactgact	tggcaccctg	gcctatggca	ttggccttcc	aggcatggta	240
tgtgcccgag	gggtcagtct	gatagagcct	aggagtggca	tcaaagtcga	aaccacagat	300
gagggcagag	atgccaaacg	gcctgcgccc	attgctctgc	gtataacgct	gcttcanact	360
ggcgatgtag	cgggtgatgt	actccacagt	gaccgggtcc	tccacagtca	gccggtggct	420
ctggcactcc	acccgggccc	tgttgatgac	tatccttgca	tcggcggtga	ggcc	474

<210> 325

<211> 532

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(532)

<223> n = A,T,C or G

<400> 325

gaggagacag	gacagagcgt	ctggagaggg	aggaggacac	cgagttcccc	gtggtggcct	60
ccaggtcctg	tgcttgcgga	gccgtccggc	ggctgggata	gagccccgac	aatgggcaac	120
gcgcaggagc	ggccgtcaga	gactatcgac	cgcgagcgga	aacgcctggt	cgagacgctg	180
caggcggact	cgggactgct	gttgagcgcg	ctgctggcgc	ggggcggtgt	caccgggcca	240
gagtacgagg	cattggatgc	actgcctgat	gccgagcgca	gggtgcgccc	cctactgctg	300
ctgggtgcagg	gcaagggcga	ggccgcctgc	caggagctgc	tacgctgtgc	ccagcgtacc	360
gcgggcgcgc	cggaccccg	ttgggactgg	cagcacgtgg	gtccgggcta	ccgggaccgc	420
agctatgacc	ctccatgccc	aggccactgg	acgcgggagg	caccgggctc	ggggaccaca	480
tgccccgggt	tgcccagact	tcagaccctg	acgaggnccg	gggccctgag	gg	532

<210> 326

<211> 322

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(322)
 <223> n = A,T,C or G

<400> 326
 caaaattaac atttttatta aatcaagtta aaaaaaatgt tcagtgtana aaagtcaaca 60
 agggtttttaa caaaaccaa atataccttt ttatacaata tatgtatata ttagcagcaa 120
 actacttctg anattctctt tcttttatgt tcttctagtt attttaaaga aagcataaac 180
 aatgtatatt agtatggaat gtcagcaa at ccactcttag tcctttattc tgtgatttgg 240
 gccttctaca aaatactttg tgattctcac taatgaatat taagaacata cccaatttta 300
 actaaaaagt agtgaaacag tg 322

<210> 327
 <211> 387
 <212> DNA
 <213> Homo sapien

<400> 327
 aaaaccgtgt actattagcc atgggtcaacc ccaccgtgtt cttcgacatt gccgtcgacg 60
 gcgagccctt gggccgcgtc tcctttgagc tgtttgcaga caagggtcca aagacagcag 120
 aaaatttttcg tgctctgagc actggagaga aaggatttgg ttataagggt tcctgctttc 180
 acagaattat tccagggttt atgtgtcagg gtgggtgactt cacacgccat aatggcactg 240
 gtggcaagtc catctatggg gagaaatttg aagatgagaa cttcatccta aagcatacgg 300
 gtcttgatcat cttgtccatg gcaaatgctg gacccaacac aaatgggttc cagtttttca 360
 tctgcactgc caagactgag tggttgg 387

<210> 328
 <211> 502
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(502)
 <223> n = A,T,C or G

<400> 328
 agcagcccgg cgcggccgcc gcgcggcgcg gcggcaaggc tccggggccag catgggggct 60
 tcgtggtgac tgtcaagcaa gagcgcggcg aggggtccac gcggggcgag aaggggtccc 120
 acgaggagga gccggtgaag aaacgcggct ggcccaaggg caagaagcgg aagaagattc 180
 tgccgaatgg gcccaaggca ccggtcacgg gctacgtgcg cttcctgaac gagcggcgcg 240
 agcagatccg cagcgcgccac ccggtatctg cctttcccga gatcaccaag atgctgggcg 300
 ccgagtggag caagctgcag ccaacggaaa agcagcggta cctggatgag gccnagagag 360
 agaagcagca gtacatgaag gagctgcggg cgtaccagca gtctgaagcc tataagatgt 420
 gcacggagaa gatccaggag aagaagatca agaaagaaga ctcgagctct gggctcatga 480
 acactcttct gaatggacac aa 502

<210> 329
 <211> 463
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(463)
 <223> n = A,T,C or G

<400> 329
 caagttgcac attttaattt acaattttta ccaataaaaa ggattagttt acaaaaaggg 60
 aagtccttta tacaaaataa ggacaatttg taaaganaat ccactgtcat gttttgcctt 120
 gtcaagtcaa aactcaaata gcttgttttg gtaaaattat tccagaaaca taatccagac 180
 aaaatcaata acgtcatcag cttcctaacc atgtttaana ggaataactt catgaacatt 240
 ttgccctgaa ctgaanagtt ctaaataactt gtaaaccttt aggaaaaaat gactgctcgc 300
 aggcagcttg actggtaaga gggtagacca nagactccgg gtcactcact gtcagaatat 360
 tcttatacat acaatgagtc tccacgcctg tacaatgagt gtcgtgcaac ataattggag 420
 taatggcctc taaaatttta caagtaaact ttattgnggc ccc 463

<210> 330
 <211> 500
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(500)
 <223> n = A,T,C or G

<400> 330
 taattataga tctacaaaat atgaaatgta ttccaagaat gcagaaaaac catctagaag 60
 caaaaggact ataaaacaaa aacagagaag aaaattcatg gctaaaccag ctgaagaaca 120
 gcttgatgtg ggacagtcta aagatgaaaa catacatata tcacatatta cccaagacga 180
 atttcaaaga aattcagaca gaaatatgga agagcatgaa gagatgggaa atgattgtgt 240
 ttccaaaaaa acagatgcc a cctgtgggaa gcaagaaaag tagcactaga aaagataagg 300
 aagaatctaa aaagaagcgc ttttccagtg agtccaagaa caaacttgtn cctgaagaag 360
 tgacttcaac tgtcacgaaa agtcgaanaa tttccangcg tccatctgat tgggtgggtgg 420
 taaaancaga ggagagtcct gtttatagca attcttcagt aagaaatgaa ttaccaantg 480
 catcacaatn ntgcccggaa 500

<210> 331
 <211> 494
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(494)
 <223> n = A,T,C or G

<400> 331
 tctctctctc tctcaaaatt acagtgttca ttgtcattga cctcagcagc aaatttgact 60
 tgaattcact taggatcgca ggaatcaggg gaaagtgatt tttaaaggagg tttctccagc 120
 acattttaag aaaagggacc aaaagttatt ttagcttcct caatagattg catgttgctt 180
 attaggataa taaattaata ttaaattgcaa tatatgtctt gnctttatta tggcatctat 240
 ttaggagttg ttcaaatac tgcagtaggg ctctgcaaat aaaataatgn aacctattat 300
 catggatcta atgnactgna actttatcag tgaaaggnaa aatctcaaat aacaagtaca 360
 aacattggac aattacctat aaagatttgt aaaaggaaaa tttttccata gatttcattc 420

ttggcatttt gtaaagacga cctgcagnc cctgtttgn aactttttta ataaaataga 480
catctgttta cttg 494

<210> 332
<211> 538
<212> DNA
<213> Homo sapien

<400> 332
aaagaacaaa tggaacgca tgggtgttct gaacaagagt ctcaaccgtg tgcatttatt 60
gggataggaa atagtgacca agaatgcag cagctaaact tggaaggaaa gaactattgc 120
acagccaaaa cattgtatat atctgactca gacaagcgaa agcacttcat gttgtctgta 180
aagatgttct atggcaacag tgatgacatt ggtgtgttcc tcagcaagcg gataaaagtc 240
atctccaaac cttccaaaaa gaagcagtca ttgaaaaatg ctgacttatg cattgcctca 300
ggaacaaagg tggctctgtt taatcgacta cgatcccaga cagttagtac cagatacttg 360
catgtagaag gaggtaattt tcatgccagt tcacagcagt ggggagcctt ttttattcat 420
ctcttggatg atgatgaatc agaaggagaa gaattcacag tccgagatgg ctacatccat 480
tatggacaaa cagtcaaact tgtgtgctca gttactggca tggcactccc aagattga 538

<210> 333
<211> 499
<212> DNA
<213> Homo sapien

<400> 333
ctcagcctgc gggactgctc ggctcggctt ctaggcgggt ttgatgaaca cctggcttta 60
ttcttgcaat gaagaaagg tctcaacaaa aaatattctc caaagcaaag ataccatcat 120
catctcactc tcctatccca tcatctatgt ccaatatgag atctaggta ctttcacctt 180
tgattggatc agagactcta ctttttcatt ctggaggaca gtggtgtgag caagttgaga 240
ttgcagatga aaacaatatg ctttttgact atcaagacca taaaggagct gattcacatg 300
caggagttag atatattaca gaggcctca ttaaaaaact tactaaacag gataatttgg 360
ctttgataaa atctctgaac ctttcacttt ctaaagacgg tggcaagaaa ttttaagtata 420
ttgagaattt ggaaaaatgt gttaaacttg aagtactgaa tctcagctat aatctaatag 480
ggaagattga aaagtcgga 499

<210> 334
<211> 561
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(561)
<223> n = A,T,C or G

<400> 334
ttcccggtag ttcagctgca catgaataga acagcaatga gagccagtca gaaggacttt 60
gaaaattcaa tgaatcaagt gaaactcttg aaaaaggatc caggaaacga agtgaagcta 120
aaactctacg cgctatataa gcaggccact gaaggacctt gtaacatgcc caaaccaggt 180
gtatttgact tgatcaacaa ggccaaatgg gacgcatgga atgcccttgg cagcctgccc 240
aaggaagctg ccaggcagaa ctatgtggat ttggtgtcca gtttgagtcc ttcattggaa 300
tcctctagtc aggtggagcc tggaacagac aggaaatcaa ctgggtttga aactctggtg 360
gtgacctccg aagatggcat cacaagatc atgttcaacc cggcccaaaa agaaaaatgc 420
cataaacact gagatgtatc atgaaattat gcgtgcactt aaagctgcca gcaaggatga 480

ctcaatcatc actgttttaa cangaaatgg tgactattac agtagtggga atgatctgac 540
taacttcnct gatattcccc c 561

<210> 335
<211> 551
<212> DNA
<213> Homo sapien

<400> 335
aagctgggtca tggctgggga gaccaccaac tcccgcggcc agcgggtgcc ccagaaggga 60
gacgtggaga tgctgtgcgg cgggccgccc tgccagggct tcagcggcat gaaccgcttc 120
aattcgcgca cctactccaa gttcaaaaac tctctgggtg tttccttcct cagctactgc 180
gactactacc ggccccgggt ctctctctctg gagaatgtca ggaactttgt ctcttcaag 240
cgctccatgg tcctgaagct caccctccgc tgccctggtec gcatgggcta tcagtgcacc 300
ttcggcggtgc tgcaggccgg tcagtaacggc gtggcccaga ctaggaggcg ggccatcatc 360
ctggccgcgcg cccctggaga gaagctccct ctgttcccgg agccactgca cgtgtttgct 420
ccccgggcct gccagctgag cgtggtgggt ggatgacaag aagtttgtga gcaacataac 480
caggttgagc tcgggtcctt tccggaccat acggtgagag aaacgatgtc cgacctgccg 540
gaagtgcgga a 551

<210> 336
<211> 540
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(540)
<223> n = A,T,C or G

<400> 336
aggtctatgt ctactgaagg caataaacga ggaatgatcc agcttattgt tgcaaggaga 60
ataagcaagt gcaatgagct gaagtcacct gggagcccc ctggacctga gctgcccatt 120
gaaacagcgt tggatgatag agaacgaaga atttcccatt ccctctacag tgggattgag 180
gggcttgatg aatcgcccag cagaaatgct gccctcagta ggataatggg taaataccag 240
ctgtccccta cagtgaatat gcccgaagat gacactgtca ttatagaaga tgacaggttg 300
ccagtgcctc ctccacatct ctctgaccag tcctcttcca gctcccatga tgatgtgggg 360
tttgtgacgg cagatgctgg tacttggggc aaggctgcaa tcagtgatcc agccgactgc 420
tctttgagtc cagatgttga tccagttctt gcttttcaac gaaaaaggat ttggacgtca 480
gaagtatgtc agaaaaacgc accaaagcaa ttttcanatg ccagtcaatt ggatttcgtt 540

<210> 337
<211> 422
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(422)
<223> n = A,T,C or G

<400> 337
gcagcaggaa cagttacagc agcagcagca acagcagctg ttgcaacagc agcaggaaca 60
attgcagcag caacaactgc agcctcctcc cctggagccc gaggaggagg aagaggtgga 120

```

gctggagctc atgccggtgg acctgggggc agagcaggag ctggagcagc agcggcagga 180
gttggagcgg cagcaggagc tggaacggca gcaggagcag cggcagctgc agctcaaact 240
gcaggaggag ctgcagcagc tggagcaaca gctggagcag cagcagcagc agctggagca 300
gcaggagggtg cagctggagc tgacccccgt ggagctaggg gccacgagcaggagggtgca 360
gctggagctg acccccgtgc agccggagct gcagctggaa ctggtgccan cccaggggggc 420
gg 422

```

```

<210> 338
<211> 601
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

```

```

<400> 338
catcttacga acgctctatg atgtcttatg agcgggtctat gatgtccctt atggctgaac 60
gctctatgat gtcagcctac gagcgctcta tgatgtcagc ctacgagcgc tctatgatgt 120
cccctatggc tgagcgctct atgatgtcag cttatgaacg ctccatgatg tcagcttatg 180
aacgctccat gatgtcccca atggctgatc gatctatgat gtccatgggt gctgaccggg 240
ctatgatgtc gtcatactct gctgctgacc ggtctatgat gtcacgtac tctgcagctg 300
accgatctat gatgtcatct tatactgctg atcgttcaat gatgtctatg gctgctgatt 360
cttacaccga ttcttacact gacacatata cagaggcata tatgggtgcca cctttgcctc 420
ctgaagagcc cccaacaatg ccaccgttgc cacctgagga gccaccaatg acaccaccat 480
tgcttctga ggaaccaccc agagggtcca gcattgcca cttgagcagt cagcattaac 540
cagcttgaaa atacttggcc ctacanangg tgccatcatt accatctgaa gagctgtatc 600
g 601

```

```

<210> 339
<211> 440
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

```

```

<400> 339
agagggagga ggcccaactg gtgatgctgc tgctgctgct gctgccgccg ccgccgcctc 60
tattgctgat actctagtgg ggctggaagg gtggttccta ttgcgaccat cgccaaccag 120
agacagaggg aaaaaaaaaa ccggcagcca ctgctgatgt tgggttcgga ggctgcatcc 180
gactcgggtc caaggaaaat ggattcagtt tgcattctct cctcctttta acagcttctc 240
cgggtctcag catggtatca aagcttgaaa gagagaagac tcaagaagcg aagaggattc 300
gtgagctgga gcagcgcaag cacacgggtg tggtgacaga actcaaagcc aagctccatg 360
aggagaagat gaaggagctg caggctgtga gggagaacct tatcaagcag cacgacagga 420
aatgtcaang acggtgaagg 440

```

```

<210> 340
<211> 450
<212> DNA
<213> Homo sapien

```

<400> 340

```
<210> 341
<211> 451
<212> DNA
<213> Homo sapien
```

<400> 341

```
<210> 342
<211> 498
<212> DNA
<213> Homo sapien
```

<400> 342

$\langle 210 \rangle$	343
$\langle 211 \rangle$	491

<212> DNA

<213> Homo sapien

<400> 343

ccgaccccta	ctcggcgggcg	caactccaca	accagtacgg	cccatgaat	atgaacatgg	60
gtatgaacat	ggcagcagcc	gcggcccacc	accaccacca	ccaccaccac	caccccggtg	120
cctttttccg	ctatatgcgg	cagcagtgca	tcaagcagga	gctaattctgc	aagtggatcg	180
accccgagca	actgagcaat	cccaagaaga	gctgcaacaa	aactttcagc	accatgcacg	240
agctgggtgac	acacgtctcg	gtggagcacg	tggcgggccc	ggagcagagc	aaccacgtct	300
gcttctggga	ggagtgtccg	cgcgagggca	agcccttcaa	ggccaaatac	aaactgggtca	360
accacatccg	cgtgcacaca	ggcgagaaaac	ccttcctctgc	ccttcggggg	gtggcaaagt	420
cttcgcgcgc	tccgagaacc	tcaagatcca	caaaaggacc	acacagggga	gaagccgtcc	480
agtggagttg	a					491

<210> 344

<211> 412

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(412)

<223> n = A,T,C or G

<400> 344

gtgcgctgtc	ttcccgccttg	cgtcagggac	ctgcccgaact	cagtggccgc	catggcatca	60
gatgaaggca	aactttttgt	tggagggctg	agttttgaca	ccaatgagca	gtcgctggag	120
caggtcttct	caaagtacgg	acagatctct	gaagtgggtg	ttgtgaaaga	cagggagacc	180
cagagatctc	ggggattttg	gtttgtcacc	tttgagaaca	ttgacgacgc	taaggatgcc	240
atgatggcca	tgaatgggaa	gtctgtagat	ggacggcaga	tccgagtaga	ccaggcaggc	300
aagtcgtcan	acaaccgatc	ccgtgggtac	cgtgggtggct	ctgccggggg	ccggggcttc	360
ttccgtgggg	gcccgangac	ggggcccgtg	ggttctctaa	aagaagaggg	ga	412

<210> 345

<211> 498

<212> DNA

<213> Homo sapien

<400> 345

aactagtctc	gggccatcct	ttctgcgcac	ccggtgtcgc	tgggctgcac	cccgggcggg	60
gacgtccgcc	gggcacggga	gggggccaaag	atgccgatca	ataaatcaga	gaagccagaa	120
agctgcgata	atgtgaagg	tgttgtagg	tgccggcccc	tcaatgagag	agagaaatca	180
atgtgctaca	aacaggctgt	cagtgtggat	gagatgaggg	gaactatcac	tgtacataag	240
actgattctt	ccaatgaacc	tccaaagaca	tttacttttg	atactgtttt	tggaccagag	300
agtaaacaac	ttgatgttta	taacttaact	gcaagacctt	ttattgattc	tgtacttgaa	360
ggctacaatg	ggactatttt	tgcatatgga	caaaccggaa	caggcaaaac	ttttaccatg	420
gaaaggtgtc	gagctattcc	tgaacttaga	ggaataattc	cccaatttct	ttgctcacia	480
tatttgggcc	atatttgc					498

<210> 346

<211> 427

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(427)
 <223> n = A,T,C or G

<400> 346
 agatggcggt cgccgtgaga actttgcagg aacagctgga aaaggccaaa gagagtctta 60
 agaacgtgga tgagaacatt cgcaagctca ccgggcggga tccgaatgac gtgaggccca 120
 tccaagccag attgctggcc ctttctgggc ctggtggagg tagaggacgt ggtagtttat 180
 tactgaggcg tggattctca gatagtggag gaggaccccc agccaaacag agagaccttg 240
 aaggggacgt cagtaggctg ggcgggggagc gtcggaccag aagagaatca cgccaggaaa 300
 gcgacccgga ggatgatgat gttaaaaagc cagcattgca gtcttcant gtagctacct 360
 cccaaagagc gcccacgta gagaccttat ccagggatca aaattttgga tgaaaaaggg 420
 gaaagcc 427

<210> 347
 <211> 280
 <212> DNA
 <213> Homo sapien

<400> 347
 cacagaaagt tctccgctcc cagacatggg tccctcggct tctgcctcg gaagcgcagc 60
 agcaggcatc gtgggaaggt gaagagcttc cctaaggatg acccgtccaa gccgggtccac 120
 ctcacagcct tcttgggata caaggctggc atgactcaca tcgtgcggga agtcgacagg 180
 ccgggatcca aggtgaacaa gaaggaggtg gtggaggctg tgaccattgt agagacacca 240
 cccatggtgg ttgtgggcat tgtgggctac gtggaaaccc 280

<210> 348
 <211> 411
 <212> DNA
 <213> Homo sapien

<400> 348
 caactatgat gtgcctgaaa aatgggcacg attctatact gcagaagtag ttcttgcatt 60
 ggatgcaatc cattccatgg gttttattca cagagatgtg aagcctgata acatgctgct 120
 ggataaatct ggacatttga agtttagcaga ttttggtact tgtatgaaga tgaataagga 180
 aggcattgta cgatgtgata cagcgggttg aacacctgat tatatttccc ctgaagtatt 240
 aaaatcccaa ggtggtgatg gttattatgg aagagaatgt gactggtggt cggttggggg 300
 atttttatac gaaatgcttg taggtgatac acctttttat gcagattctt tggttggaac 360
 ttacagtaaa attatgaacc attaaaaatt cacttacctt tctgatgat a 411

<210> 349
 <211> 408
 <212> DNA
 <213> Homo sapien

<400> 349
 gatgggcacg tctcggggaca actggcacaa gcgcccga aa accgggggca agagaaagcc 60
 ctaccacaag aagcgggaagt atgagttggg gcgcccagct gccaacacca agattggccc 120
 ccgcccacat cacacagtcc gtgtgcgggg aggttaacaag aaataccgtg ccctgaggtt 180
 ggacgtgggg aatttctcct ggggctcaga gtgttggtact cgtaaaacaa ggatcatcga 240
 tgttggtctac aatgcatcta ataacgagct ggttcgtacc aagaccctgg tgaagaattg 300
 catcgtgctc atcgacagca caccgtaccg acagtggtag gagtcccact atgcgctgcc 360
 cctgggcccgc aagaaggag ccaaactgac ttctgaggaa gaagaaaa 408

<400> 350

<210> 351

<211> 226

<212> DNA

<213> Homo sapien

<400> 351

<210> 352

 $\langle 211 \rangle$ 410

<212> DNA

<213> Homo sapien

<400> 352

<210> 353

<211> 380

<212> DNA

<213> Homo sapien

 $\langle 220 \rangle$

<221> misc feature

<222> (1) ... (380)

<223> n = A, T, C or G

<400> 353

gagttttat	agaaagtatc	atagtgtaaa	caaacaaatt	gtaccacttt	gatttttcttg	60
gaatacaaga	ctcgtgatgc	aaagctgaag	ttgtgtgtac	aagactcttg	acagttgtgc	120
ttctctagga	ggntggggtt	ttttaaaaaa	agaattatct	gngaaccata	cgtgattaat	180

```

aaagatttcc tttaaggcan aggctggctn agatgctgct gttatcttct gcctcagaca 240
gacagtataa gnggtcttgt ttctaagatt cctaccacca gttactttgg gccaagtatc 300
cacatcccct tgcgtatggg agnggggtga anagtgttgg atgcaaagng gttattatgg 360
gaagnagctc natggtaaaa 380

```

```

<210> 354
<211> 379
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(379)
<223> n = A,T,C or G

```

```

<400> 354
caacacatct ttattaaaca cctgaagtta ctgggaggag gccatgatgc tggacacact 60
gtcaaagtca atcttctcca caatgttctt gggtttaatg ctctcttctt ggctacagan 120
gaanatctgc cccgactngt cggcactcca gccgtatttg ctcattccaca ccttttagctg 180
gctgtccgac aganccccga gcatntcggc cagcagccan cggncaatgt gctggtaagt 240
gatacccaca acatggcaga taaactttcg gacanagtct tcaaagccag ttataccttc 300
caagagggtc atgttttcat ccagggttg ccanaagcct ggaaatggca ggtctccaac 360
aggtccccca ggtacaaaa 379

```

```

<210> 355
<211> 499
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(499)
<223> n = A,T,C or G

```

```

<400> 355
gtccagagct gctggtgctc ccgttccccca gaccctaccc ctatccccag tggagccgga 60
gtgcggggcg gccccaccac cgccctcacc atggtgctgt tggcagcagc ggtctgcaca 120
aaagcaggaa aggctattgt ttctcgacag tttgtggaaa tgaccogaac tcggattgag 180
ggcttattag cagcttttcc aaagctcatg aacactggaa aacaacatac gtttggtgaa 240
acagagagtg taagatatgt ctaccagcct atggagaaac tgtatatggt actgatcact 300
acaaaaaaca gcaacatttt agaagatttg gagaccctaa ggctcttctc aagagtgatc 360
cctgaatatt gcgagcctta gaagagaatg aaatatctga gcactgnntt gatttgattt 420
ttgcttttga tgaaaatgtc gcactgggat acccgggang aatgttaact tggcacagat 480
canaaccttt cacagaaaa 499

```

```

<210> 356
<211> 511
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

```

<400> 356

```

gggcttctgc tgagggggca ggcggagctt gaggaaaccg cagataagtt tttttctctt    60
tgaaagatag agattaatac aactacttaa aaaatatagt caataggtta ctaagatatt    120
gcttagcggt aagtttttta cgtaatttta atagcttaag attttaagag aaaatatgaa    180
gacttagaag agtagcatga ggaaggaaaa gataaaaggt ttctaaaaca tgacggaggt    240
tgagatgaag cttcttcatg gagtaaaaaa tgtattttaa agaaaattga gagaaaggac    300
tacagagccc cgaattaata ccaatagaag ggcaatgctt ttagattaaa atgaagggtga    360
cttaaacagc ttaaagttta ntttaaaagt tgtaggtgat taaaataatt tgaaggcgat    420
cttttaaaaa gagattaaac ccgaagggtga ttaaaagacc ttgaaatcca tgacgccagg    480
gagaattgcc gtcattttaa gcctagttaa c                                     511

```

<210> 357

<211> 511

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(511)

<223> n = A,T,C or G

<400> 357

```

gatacttcac atttccctag ggacgggagc ccgaggggtc cgttcggccc tcttcctctc    60
gctggggcca caccgcgtg taggaccgta acccttagtc ccaatgcctc cgtaagcgga    120
gttgagtggg tgcctgtggt tggagctgtg gaggtgtccc cgggtggcgag cgcggccaga    180
actgcggtca cttaagtttt ccgtgtgcgg gttgcaagga gcgtgcgtgc gtctggtata    240
atttggcttc ctgagattct gcttacaaga aaggagtggg aaataccctt ggaaagaaaa    300
ctaaaacagt aagaaaacca aaacttattt ttacatggnt gtcagcacat ttaccgatat    360
ggacactttt cccaataatt tcctcctggg ggagacagtg gattgacagg ttctcagtcg    420
gaattccaga aaaatgttaa ttgatgaaaa gggtagcnatg tgagcatcat aaagntaatt    480
attaanacac tgaaggctga acacacaagg g                                     511

```

<210> 358

<211> 401

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(401)

<223> n = A,T,C or G

<400> 358

```

acggatgaag atgatgacct tcaagaaaat gaagacaata aacaacataa agaaagcttg    60
aaaagagtga cctttgcttt accagatgat gcggaaactg aagatacagg tgtttttaat    120
gtaaagaaaa attctgatga agttaaatcc tcctttgaaa aaagacagga aaagatgaat    180
gaaaaaattg catctttaga aaaagagttg ttagaaaaaa agcccgtggc agcttcaggg    240
ggaagtgaca gcacagaaga ggccagagaa cacctcctgg aggagaccct acctttgcca    300
tctgcccgat ggccctgtga ttacagagga acccccttca ctggagattt ctttaacnga    360
ngatagagat cngnttggga tatgtntcct taagaaaacc t                                     401

```

<210> 359

<211> 511

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 359

gcgatgcccc	cgcgcccagg	acgcctcctc	ccgctgctgg	cccggccggc	ggccctgact	60
gcgctgctgc	tgctgctgct	gggccatggc	ggcggcgggc	gctggggcgc	ccgggcccag	120
gagggcgcg	cgggcgcggc	ggacggggcc	cccgcggcag	acggcgagga	cggacaggac	180
ccgcacagca	agcacctgta	cacggccgac	atgttcacgc	acgggatcca	gagcgcccgc	240
gcacttcgtc	atgttccttcg	cgccctgggtg	tggacacttg	ccagcggctt	gcagccgant	300
ttggaatgac	cttggganga	acaaatacaa	cagcatggaa	agaatgccaa	aagtctatgt	360
ggnttaaagt	ggacttgcac	nggccacttc	gactngtgct	cccccaagg	gngggaagat	420
accacacctta	aaacttttca	accaagccaa	aaactttgaa	aaccaggtct	cggattcaaa	480
atggaaaact	gatgttcaac	ctgaacaaga	a			511

<210> 360
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 360

tactgggaga	ctttgagatt	gagtcctaac	agctggaagc	agagtcttgg	agtcggataa	60
tagacagcaa	gtttctaaaa	cagcaaaaga	aagatgtggt	caaacggcaa	gaagtaatat	120
atgagttgat	gcagacagag	tttcatcatg	tcccgactct	caagatcatg	agtgggtgtg	180
cnagccnggg	gatgatggcg	gatctgnttt	ttgagcanca	gatggtagaa	aaagctgggt	240
ccctgttttg	atgagcttga	tcagtatccc	atacccttcc	tttccagagg	attcttggag	300
ccggaaagaa	nggagtcttc	ttggtgggat	aaaaagttaa	aaagaacttt	ctcttcaana	360
aggatagggg	gatgtgcttt	gtaaaatcan	tttttcaggg	ngganaatgc	cnnaaccgtt	420
ttaaagaaaa	acatnttggg	naagtttttg	tgggccaaca	ttaccgggtc	ttgtaaacct	480
accttcaaag	aacctttttg	cccagggtta	a			511

<210> 361
<211> 411
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(411)
<223> n = A,T,C or G

<400> 361

gctcagcggc	ccgatccac	ggaagcgcg	tcggaggggt	gggaccggc	cggaccggag	60
atggcgccgc	cagcgggcgg	ggcggcggcg	gcggcctcgg	acttgggctc	cgccgcagtg	120
ctcttggtg	tgcacgccgc	ggtgaggccg	ctgggcgcgc	ggccagacgc	cgaagcacia	180

cttgcgagg	ctgcagctta	acgcggaccc	tgagaagcct	ggcgcttncn	gctggaactt	240
cttggcgcg	gacctggggc	ggtaatttga	gtggccctga	gtcatttcta	caccatccag	300
gcccaccaca	cgactaagct	cacaagaagg	ctgaactnnc	tgattctnaa	cctagaanta	360
cgtgcatcta	tcagtgccng	aagaaatgac	aacataccac	tggaactct	g	411

<210> 362
 <211> 511
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(511)
 <223> n = A,T,C or G

<400> 362						
cgggggaccg	ggctgccttg	gcccctcagc	gctcgcgctct	tttccggcag	ttggaacgct	60
tcctgttgtc	ctcaccgcga	accgcctggt	gcccctgtgc	tcagagtcct	tcacgcgtcc	120
cctcccgtct	ttggctcggt	ggctgccgcc	gcgggggctt	cgccagcctt	caagtcgaga	180
ctactggccg	aaggggcgtc	tgcggtcttc	cgccgtcccc	agccctgcct	ctccctgggc	240
tctgccatgg	caatgacagg	ctcaaacact	tgctcatcca	tgagtaacca	cacaaaggaa	300
agggtgacaa	tgaccaaaaag	tgacactgga	gaatttttat	agcaacctta	tcgctcacat	360
gaagaacgag	aaatgagaca	aaagaagtta	gaaaaagggg	atggaagaag	aaggcctaaa	420
aaaatgaagg	agaaaaccaa	cttccgaaga	tcaaccacat	tgcttcggaa	anggaacaaa	480
aantttcttt	cgtttgaaan	aaaaacaaan	a			511

<210> 363
 <211> 401
 <212> DNA
 <213> Homo sapien

<400> 363						
caggatctgg	ggagaaagag	ccccatccct	tctctctctg	ccaccatttc	ggacaccccg	60
cagggactcg	ttttgggatt	cgcactgact	tcaaggaagg	acgcgaaccc	ttctctgacc	120
ccagctcggg	cggccacctg	tctttgccgc	ggtgaccctt	ctctcatgac	cctgcggtgc	180
cttgagccct	cggggaatgg	cggggaaggg	acgcggagcc	agtgggggac	cgcgggggtc	240
gcgaggagc	catccccgca	ggcggcgcgt	ctggcggaagg	ccctgcggga	gctcgggtcag	300
acaggatggt	actggggaag	tatgactggt	aatgaagcca	aagagaaatt	aaaagaggca	360
ccagaaggaa	ctttcttgat	tagagatagc	tcgcattcag	a		401

<210> 364
 <211> 401
 <212> DNA
 <213> Homo sapien

<400> 364						
agtcaaaggt	ttctttttccc	tttttaccat	ggtttctaca	aaaataacct	tcaggaaaaa	60
gaaaatcagg	aaaaaaattt	tttttcaata	atcttattcc	ctatatataa	ttagatttga	120
agaggattaa	cgttgtttta	gtttgggtcc	agatcagcct	tataacaacat	ttctaaactc	180
atttgacttt	ttaaaaaatt	taaacacaga	cttctaaaat	tacttgatgt	aagtaattta	240
aatcacttat	gaccaagtta	ttaaccttat	gaatcagaag	tctgaccctt	gtaggaaatt	300
atattcacat	ataaagtaca	tcagatcttt	gccatatatt	gatgggttatt	atgcataaac	360
acattgagtt	gtgttggaag	cagatttata	aacctgcatg	t		401

<210> 365
 <211> 361
 <212> DNA
 <213> Homo sapien

<400> 365
 atctggagtt gcacaaatag ttcttttagaa cataaaaacta aatggattta tacataacag 60
 ttacattcag catttaagag aggcagtaca aaaatgtggt ctgcttttat ctgatataaa 120
 ttgcatgtaa taccatgatt taaacaatat cagttatatt aactaatgcc atgagatata 180
 tcttactcag aacgtctgat gtttcccata atagacagaa aaaatgcagt tgtatgagca 240
 actgagtttc ttttcatctt caaattcatt tgtgatggtg ggaagatcta aggacaatcc 300
 ttccattgaa gaagtaggaa aaacagttca gcactgttct gaactcatca aaaatgaaat 360
 t 361

<210> 366
 <211> 401
 <212> DNA
 <213> Homo sapien

<400> 366
 cgggagcagc agaggtctag cagccgggcg ccgcggggcg ggggcctgag gaggccacag 60
 gacgggcgtc ttcccggcta gtggagcccg gcgcggggcg cgctgcggcg gcaccgtgag 120
 gggaggaggc cgaggaggac gcagcgcccg ctgccggcgg gaggaagcgc tccaccaggg 180
 ccccgacgg cactcgttta accacatccg cgctctgctt ggaaacgctt gctggcgctt 240
 gtcaccggtt ccctccattt tgaaagggaa aaaggctctc cccacccatt ccctgcccc 300
 taggagctgg agccggagga gccgcgctca tggcgttcag cccgtggcag atcctgtccc 360
 ccgtgcagtg ggcgaaatgg acgtgggtctg cggtaacgcgg c 401

<210> 367
 <211> 401
 <212> DNA
 <213> Homo sapien

<400> 367
 catggagtcg ggcaagatgg cgcctcccaa gaacgctccg agagatgcct tggatgatggc 60
 acagatcctg aaggatatgg gaatcacaga gtatgaacca agggttataa atcaaatggt 120
 ggaatttgct ttccggttatg tgactacaat tctggatgat gcaaaaattt attcgagcca 180
 tgctaagaaa cctaattgtg atgcagatga tgtgagactg gcaatccagt gtcgtgctga 240
 ccaatctttt acctctctc cccaagaga ttttttactg gatatcgcaa ggcagaaaaa 300
 tcaaaccctt ttgccactga ttaagccata tgcaggacct agactgccac ctgatagata 360
 ctgcttaaca gtcctaaact ataggctgaa gtccttaatt a 401

<210> 368
 <211> 401
 <212> DNA
 <213> Homo sapien

<400> 368
 cggagcggta ggagcagcaa tttatccgtg tgcagcccca aactggaaag aagatgctaa 60
 ttaaagtga gacgctgacc ggaaaggaga ttgagattga cattgaacct acagacaagg 120
 tggagcgaat caaggagcgt gtggaggaga aagagggaat cccccacaa cagcagaggc 180
 tcatctacag tggcaagcag atgaatgatg agaagacagc agctgattac aagattttag 240
 gtggttcagt ccttcacctg gtgttggctc tgagaggagg aggtggtctt aggcagtgat 300

ggaccctcca ttttacctct ttaccctgtc gtcataatg aggcatacata tatcctctca 360
ctctctggga caccatagcc ctgccccctc ccttgatgc c 401

<210> 369
<211> 174
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(174)
<223> n = A,T,C or G

<400> 369
gagagnggg cgccaagcgc ggggcccggag cggccttccc ggagtccttt gcgcggcacc 60
tggcgacaaa atggctgccc gagggagacg ggcggagcct cagggccggg aggctccggg 120
ccccgcgggc ggtggcggtg gcgggagccg ttgggctgag tcgggatcgg ggac 174

<210> 370
<211> 375
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(375)
<223> n = A,T,C or G

<400> 370
tgcttttcca actttattta gaaaaacaaa tccagggtccc agtgccccct gtaccctccc 60
cgacccccagc cataatttaa ataacttana gacagagttg gagggagggg acagganagg 120
ttgggggtcac ggtggaagga ggaaganagc ccactacagc cgccgcagcg cccgcttctt 180
gtccgtcttt ttcttgcccg ccagcttctt atcgcgctcg ccagcatgct tnttggccat 240
gggaccctca gcccctcccg ggccccctgg ggccccaggg tcggtggagg aagcttcagt 300
gccactggcc agggcccagc cggcttcggc cctgccgctg ggcccgcggg cgcccccggtg 360
gatctctgtg agcag 375

<210> 371
<211> 375
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(375)
<223> n = A,T,C or G

<400> 371
taaattctaa aaaatatattt aatacttgaa aacttctaaa acaaaaaggta aggtaacatg 60
ttctttcaaa agtgaatttc acatgcaaac cattaattat atttatattta ctgngagata 120
aaagcaaaaac ataacattcg gagaaagaga ccagtaactg acctatttat tttatattat 180
attaatgnga atcctcatta gaaatgtgat aacgttattg cacaaacaaa accgtgggca 240
gaaacatccc agcaatgcag gggcgcccat accgggttac aagggatgtc cagcatgtgt 300
ttccctggaa cactcanagt ctgcactttt cctgcaaagt ggaccatgtc tgattattta 360

375

<400> 372

<400> 373

<400> 374

<400> 375

gagcggagtc cgctggetga cccgagcgct ggtctccgcc gggaaccctg gggcatggag 60
aggtctgagt acctcggccg cggcgcacgc tgcctcgcgg agccaggccg aggacgtgag 120
ggtggagggc tcctttcccg tgaccatgct tccgggagac ggtgtggggc ctgagctgat 180

```
<210> 376
<211> 284
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(284)
<223> n = A,T,C or G
```

<400> 376

ggaacaaggt	cgtgaaaaaa	aaggtcttgg	tgaggtgccg	ccatttcatt	tgctctcatt	60
ctctgcgcct	ttcgagagc	ttccancagc	tggtatgttg	ggccagagca	tcgggaggtt	120
cacaacctct	gtggtccgta	ggagccacta	tgaggagggc	cctgggaaga	atttgccatt	180
ttcagtggaa	aacaagtggg	cgttactagc	taagatgtgt	ttgtactttg	gatctgcatt	240
tgctacaccc	ttccttggtan	taagacacca	actgcttaaa	acat		284

```
<210> 377
<211> 401
<212> DNA
<213> Homo sapien
```

<400> 377						
atztatgtta	ttgcactctc	ggtgtgattt	atcgtatgta	tctgataggt	tttatgaatt	60
gttttgagtt	gtaaactcct	atacccttta	ttaaaatgga	cctaattaag	tgattttatgc	120
tttgtgcaat	ttcttaaate	agatctctct	aggattgaag	ggatccatag	gtatctttca	180
cttagtgtga	agcctagtag	tatactttta	tattcctgaa	gagagaccag	cattaacata	240
aagagagaag	tcttaggaaa	aatatacct	aagaattatt	tttaaaattc	atactgtgaa	300
ggagaatctg	cctgcctatt	tcctctccaa	atttcagaaa	ataacacaga	gtgctatttg	360
cctgaacttt	aatgagcttg	actttgttat	gattcagqqa	g		401

```
<210> 378
<211> 401
<212> DNA
<213> Homo sapien
```

<400> 378						
ccagaacaca	ggtgtcgtga	aaactacccc	taaaagccaa	aatgggaaag	gaaaagactc	60
atatcaacat	tgtcgtcatt	ggacacgtag	attcgggcaa	gtccaccact	actggccatc	120
tgatctataa	atgcggtggc	atcgacaaaa	gaaccattga	aaaatttgag	aaggaggctg	180
ctgagatggg	aaagggctcc	ttcaagtatg	cctgggtctt	ggataaactg	aaagctgagc	240
gtgaacgtgg	tatcaccatt	gatatctcct	tgtggaaatt	tgagaccagc	aagtactatg	300
tgactatcat	tgatgcccca	ggacacagag	actttatcaa	aaacatgatt	acaggggacat	360
ctcaggctga	ctgtgctgtc	ctgattgttg	ctgctggtgt	t		401

```
<210> 379
<211> 401
<212> DNA
<213> Homo sapien
```

<400> 379

tcagatatca	ggtggcttct	tcaaatgatt	tttaagtatc	tcgatgatga	tgaagaacaa	60
agacatcaat	caggattcag	gaagacagct	tttgcggaag	atgcttaaag	ggaagcatca	120
aggattggtg	ttgatatttg	aaagttaaag	agtgggtatac	ttttattcag	tcaacacatg	180
acaaatgtaa	aaggcactca	tttggtgttc	ctggaagaag	cctggcagca	ttccattcag	240
acatctgccc	tttcatcgtc	ccacttttta	cttattgcag	tcctttcagt	ctgaatattt	300
cctcctgacg	catcttctgc	cgtccgaaat	gactccctgc	tcccagatcc	tgtagccctt	360
attattgaca	cctttcattt	agaaatttag	cacatgtcac	a		401

<210> 380

<211> 401

<212> DNA

<213> Homo sapien

<400> 380

cctgactctc	tgaggctcat	tttgcagttg	ttgaaattgt	ccccgcagtt	ttcaatcatg	60
tctgaaccaa	tcagagtcct	tgtgactgga	gcagctggtc	aaattgcata	ttcactgctg	120
tacagtattg	gaaatggatc	tgtctttggt	aaagatcagc	ctataattct	tgtgctgttg	180
gatatcacc	ccatgatggg	tgtcctggac	ggtgtcctaa	tggaactgca	agactgtgcc	240
cttccccctc	tgaaagatgt	catcgcaaca	gataaagaag	acgttgcctt	caaagacctg	300
gatgtggcca	ttcttgtggg	ctccatgcc	agaaggggaag	gcatggagag	aaaagattta	360
ctgaaagcaa	atgtgaaaat	cttcaaatcc	caggggtgcag	c		401

<210> 381

<211> 401

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(401)

<223> n = A,T,C or G

<400> 381

ggggcttcgc	tggcagtcct	aacggcaagc	ttgagcaacg	cggtaaaaat	attgcttcgg	60
tgggtgacgc	ggtacagctg	tccaagggcn	ttngtaacgg	gaatgccgaa	gcgtgggaaa	120
aagggagcgg	tggcggaaga	cggggatgag	ctcaggacag	agccagaggc	caagaagagt	180
aagacggccg	caaagaaaaa	tgacaaagag	gcagcaggag	agggcccagc	cctgtatgag	240
gacccccag	atcagaaaac	ctcaccagct	ggcaaacctg	ccacactcaa	gatctgctct	300
tggaaatgtg	atgggcttcg	agcctggatt	aagaagaaag	gattagattg	ggtaaaggaa	360
gaagccccag	atatactgtg	ccttcaagag	accaaattgt	c		401

<210> 382

<211> 491

<212> DNA

<213> Homo sapien

<400> 382

gagcagcccc	cggcggctga	aagccggggc	agaagtgctg	gtctcggtcg	ggattccggg	60
cttgggtccc	ccgaggcggc	gactgcggta	ggagggaaga	ggttttggac	gcgctggcct	120
cccgcgcgtg	tgcattgcag	cattatttca	gttcaaaatg	aactatatgc	ctggcaccgc	180
cagcctcatc	gaggacattg	acaaaaagca	cttgggttctg	cttcgagatg	gaaggacact	240
tataggcttt	ttaagaagca	ttgatcaatt	tgcaaactta	gtgctacatc	agactgtgga	300

gcgtattcat	gtgggcaaaa	aatacgggtga	tattcctcga	gggatttttg	tggtcagagg	360
agaaaatgtg	gtcctactag	gagaaataga	cttggaagag	gagagtgaca	cacccctcca	420
gcaagtatcc	attgaagaaa	ttctagaaga	acaaaggggtg	gaacagcaga	ccaagctgga	480
agcagagaag	t					491

<210> 383

<211> 491

<212> DNA

<213> Homo sapien

<400> 383

gagtccatct	cagcgccttg	aaaatgcagt	gaaaaaacct	gaagataaaa	aggaagtttt	60
cagacccctc	aagcctgctg	gcgaagtggg	tctgaccgca	ctggccaaag	agcttcgagc	120
agtggagat	gtacggccac	ctcaciaagt	aacggactac	tcctcatcca	gtgaggagtc	180
ggggacgacg	gatgaggagg	acgacgatgt	ggagcaggaa	ggggctgacg	agtccacctc	240
aggaccagag	gacaccagag	cagcgtcatc	tctgaatttg	agcaatgggtg	aaacggaatc	300
tgtgaaaacc	atgattgtcc	atgatgatgt	agaaagtggg	ccggccatga	ccccatccaa	360
ggagggcact	ctaactgtcc	gccagagtac	agttgaccaa	aagcgtgcca	gccatcatga	420
gagcaatggc	tttgccggtc	gcattcacct	cttgccagat	ctcttacagc	aaagccattc	480
ctcctccact	t					491

<210> 384

<211> 491

<212> DNA

<213> Homo sapien

<400> 384

gagcctaate	tcagggtggc	cacccgagac	cccttgagca	ccaaccctag	tccccgcgc	60
ggccccttat	tcgctccgac	aaggtacaaa	aaggctcttg	acggcggcgt	ggtaggagga	120
cgggagcggg	ggcgggaagt	tccttgaagg	agcgagacag	ggagggacag	ggcagaggag	180
gagaggaagg	cgatgcgacg	gacagggcga	cccgctcagg	ctgactctcg	ggggcgaggt	240
cgagccaggg	gcggtgccc	tgggggagag	gcgacgctgt	ctcaacctcc	acctcgcggc	300
ggaacccgag	gacaggagcc	tcagatgaaa	gaaacaatca	tgaaccagga	aaaactcgcc	360
aaactgcagg	cacaagtgcg	cattgggtggg	aaaggaactg	ctcgagagaa	gaagaagggtg	420
gttcatagaa	cagccacagc	agatgacaaa	aaacttcagt	tctccttaaa	gaagttagggtg	480
gtaaacaata	t					491

<210> 385

<211> 483

<212> DNA

<213> Homo sapien

<400> 385

agccgctgcg	aaggagccg	ccgccatgtc	tgcgcatctg	caatggatgg	tcgtgcgga	60
ctgctccagt	ttcctgatca	agaggaataa	gcagacctac	agcactgagc	ccaataactt	120
gaaggcccg	aattccttcc	gctacaacgg	actgattcac	cgcaagactg	tgggcgtgga	180
gccggcagcc	gacggcaaag	gtgtcgtggg	ggtcattaag	cggagatccg	gccagcggaa	240
gcctgccacc	tcctatgtgc	ggaccacat	caacaagaat	gctcgcgcca	cgctcagcag	300
catcagacac	atgatccgca	agaacaagta	ccgccccgac	ctgcgcatgg	cagccatccg	360
cagggccagc	gccatcctgc	gcagccagaa	gcctgtgatg	gtgaagagga	agcggacccg	420
ccccaccaag	agctcctgag	ccccctgccc	ccagagcaat	aaagtcagct	ggctttctca	480
cct						483

<210> 386

<211> 491
 <212> DNA
 <213> Homo sapien

<400> 386

aggtggaagg	aaaaaacata	aatgaagtta	atgcacttct	tttcctagcc	caaaagtcac	60
tgtgattata	ttttttta	gaagtttaga	aaaaaagctg	ttgtcttctc	aattgtaaaa	120
ttagtttcaa	aatgctgctt	ctcttatcat	tagtctagta	attggtgaac	ttttctgcaa	180
actgcatttt	acaaaattga	aacttggaag	ctgtattaac	ttttatagtt	aaacattgta	240
ttaaataaac	tatactataa	taaacagttt	ggttttgtat	tttttaaatt	gtattatcca	300
gcctttttaa	aattaaaagc	taaataatga	aaataaacca	attaaaacat	acttttactc	360
tcagatatatac	aggtatttac	attatgaaaa	aactgaacaa	agttttaaca	atactgagct	420
ttaagaatttt	agccagcagg	gaaaattttc	aggtttgaga	atgtttcta	gtaaatat	480
aatcataata	c					491

<210> 387
 <211> 491
 <212> DNA
 <213> Homo sapien

<400> 387

ccacaccacc	gtgtcccaag	tccagccccc	tccctccaag	gcatcagcac	ctgaaccccc	60
tgcagaagaa	gaagtggcaa	ctggtacaac	ctcagcctct	gatgacctgg	aagccctggg	120
tacactgagc	ctggggacca	cagaggagaa	ggcagcagct	gaggcggctg	tgcccaggac	180
cattggggcc	gagctgatgg	agctgggtgc	gagaaacact	ggcctgagcc	acgaattatg	240
ccgggtggcc	atcggcatca	tagtgggtca	catccaggcc	tcgggtgccg	ccagctcacc	300
agtcattggag	caggtcctcc	tctcactcgt	agagggcaag	gacctcagca	tggccctgcc	360
ctcagggcag	gtctgccacg	accagcagag	gctggagggtg	atctttgcag	acctggctcg	420
ccggaaggac	gacgcccagc	agcgcagttg	ggcactatat	gaggatgagg	gtgtcatccg	480
ctgctaccta	g					491

<210> 388
 <211> 491
 <212> DNA
 <213> Homo sapien

<400> 388

gagactatca	aactcctgag	ccaacaactt	aatatgacta	gcttacacaa	tagcttttat	60
agtaaagata	cctctttacg	gactccactt	atgactccct	aaagcccatg	tcgaagcccc	120
catcgctggg	tcaatagtag	ttgccgcagt	actcttgaaa	ctaggcggct	atggtataat	180
acgcctcaca	ctcatttctca	accccctgac	aaaacacata	gcctaccctt	tccttgtact	240
atccctatga	ggcataatta	taacaagctc	catctgccta	cgacaaacag	acctaaaatc	300
gctcattgca	tactcttcaa	tcagccacat	agccctcgta	gtaacagcca	ttctcatcca	360
aaccccctga	agcttcaccg	gcgagtcac	tctcataatc	gccacggac	ttacatcctc	420
attactattc	tgcctagcaa	actcaaacta	cgaacgcact	cacagtcgca	tcataatcct	480
ctctcaagga	c					491

<210> 389
 <211> 511
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature

<222> (1)...(511)

<223> n = A,T,C or G

<400> 389

tactgatatc	tctttaatac	tttcatcatt	caagtttggt	canaacatta	caagaggcat	60
gaaagaaaaa	ataattccat	ttttaaaact	ctgtctgtcc	aaagtataac	atatgaaacc	120
atgccattat	ctnttaggaa	acaaaagcat	tcaaaattaa	tttggtatta	aagttcaaga	180
ttcanactaa	cctcaaagta	cggcatgtgc	agtgtttaag	tgcaanaagt	attttcattc	240
caattatttt	acananatgc	tggagtgcgc	tgtgcaattt	gaaatattca	aatcctttta	300
ggnttctgaa	ctaagtgttt	aaatgaaaac	tgaaatgctg	catagtttca	gtggctttca	360
atttcctggt	tgatctcaga	aatatatgga	tgatctttgc	cgtgagctac	ttccatgatt	420
gcaatggcct	tcttcagggc	tttctcccct	gcggctttgt	gttccaggcc	catgtagagt	480
ctccctagct	tcaaccacat	ggaggccacg	t			511

<210> 390

<211> 1984

<212> DNA

<213> Homo sapien

<400> 390

cctgggggta	gaggctgggg	tgggtggggg	gtaagggggc	agtccttctc	cccttcgacg	60
gcggctccga	gtccagcccc	ttccttcccc	cgtcgcctcg	cccggccccc	agccccctca	120
tgagggtgtc	cgtgccgggt	ccggcggccg	ctgccgcccc	cgcagccggc	cgcgagccct	180
ccacgcccgg	cgggggcagc	ggaggcggag	gcgcgctcgc	tgacgacctc	ggcgccgcgg	240
tgccgggctc	cgtgcagttg	gcgctgagcg	tcctgcacgc	cctgctctac	gccgcgctgt	300
tcgcctttgc	ctacctgcag	ctgtggcggc	tgctcctgta	ccgcgagcgg	cggctgagtt	360
accagagcct	ctgcctcttc	ctctgtctcc	tgtgggcagc	gctcaggacc	accctcttct	420
ccgcgcctt	ctcgctcagc	ggctccctgc	ccttgctccg	gccgcccgt	cacctgcact	480
tcttccccca	ctggctgctc	tactgcttcc	cctcctgtct	ccagttctcc	acgctctgtc	540
tcctcaacct	ctacctggcg	gagggtatat	gtaaagtcag	atgtgccact	gaacttgaca	600
gacacaaaat	tctactgcat	ttgggcttta	taatggcaag	cctgctcttt	ttagtggtga	660
acttgacttg	cgcaatgcta	gttcatggag	atgtcccaga	aaatcagttg	aagtggactg	720
tgtttggtcg	agcattaatt	aatgatagcc	tgtttattct	ttgtgccatc	tcttttagtgt	780
gttacatatg	caaaattaca	aaaatgtcat	cagctaattg	ctacctcgaa	tcaaagggta	840
tgtctctgtg	ccagactgtc	atcgtgggct	ctgtagtcat	tcttctgtac	tcttccagag	900
cttggttata	tttgggtggt	gtcaccatat	ctcaggatac	attagaaagt	ccattttaatt	960
atggctggga	taatctttca	gataaggctc	atgtagaaga	cataagtggg	gaagagtata	1020
tagtatattg	aatggtcttc	tttctgtggg	aacatgtgcc	agcatggctg	gtgggtactgt	1080
ttttccgggc	acagagatta	aaccagaatt	tggcacctgc	tggcatgata	aatagtcaca	1140
gttatagttc	cagagcttac	tttttcgaca	atccaagacg	atatgatagt	gatgatgacc	1200
tgccaagact	gggaagtcca	agagaaggaa	gtttaccaaa	ttcgcaaagt	ttgggctggt	1260
atggcaccat	gactgggtgt	ggcagcagca	gttacacagt	cactccccac	ctgaatggac	1320
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atagcttata	tgtgacacca	caaaactgac	agcatcacca	agtcattgatt	cttgagttgt	1440
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tgttgcaact	gaaaacaaaa	tctggaagtg	tggctgtgtt	tggtaaataa	cacagctatt	1560
atttttgacc	tcttcatagt	aaaatgaagt	aaaatggaaa	gtttggagta	ggagaaaaga	1620
gagattagat	cttaaggcac	ttgatggcct	ccaaaaatcc	tgactttgga	acatcaaata	1680
catatgtgca	cttttatctt	tgttctgagt	cactgcagtc	cccaaagtca	tatgccaatg	1740
ttcacactga	aatactgtat	tgtacaccaa	actggaaggc	aattttccta	tgaaaatcaa	1800
agccggtata	ttcattggta	tgctctatac	agatatctta	ataaaaatct	tatagtgtga	1860
acagtgcaca	gagttaaggc	ataaaaatgt	atcattcttt	ataaaaatct	actgaaaatg	1920
tgtaatcatt	gaagacagtt	cttttaagca	tgatttttaa	atagcaactg	aaattcaatc	1984
at						

<400> 391															
Met	Arg	Val	Ser	Val	Pro	Gly	Pro	Ala	Ala	Ala	Ala	Ala	Pro	Ala	Ala
				5					10					15	
Gly	Arg	Glu	Pro	Ser	Thr	Pro	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ala
			20					25					30		
Val	Ala	Ala	Ala	Ser	Gly	Ala	Ala	Val	Pro	Gly	Ser	Val	Gln	Leu	Ala
		35					40					45			
Leu	Ser	Val	Leu	His	Ala	Leu	Leu	Tyr	Ala	Ala	Leu	Phe	Ala	Phe	Ala
	50					55					60				
Tyr	Leu	Gln	Leu	Trp	Arg	Leu	Leu	Leu	Tyr	Arg	Glu	Arg	Arg	Leu	Ser
65					70					75					80
Tyr	Gln	Ser	Leu	Cys	Leu	Phe	Leu	Cys	Leu	Leu	Trp	Ala	Ala	Leu	Arg
				85					90					95	
Thr	Thr	Leu	Phe	Ser	Ala	Ala	Phe	Ser	Leu	Ser	Gly	Ser	Leu	Pro	Leu
			100					105					110		
Leu	Arg	Pro	Pro	Ala	His	Leu	His	Phe	Phe	Pro	His	Trp	Leu	Leu	Tyr
		115					120					125			
Cys	Phe	Pro	Ser	Cys	Leu	Gln	Phe	Ser	Thr	Leu	Cys	Leu	Leu	Asn	Leu
	130					135					140				
Tyr	Leu	Ala	Glu	Val	Ile	Cys	Lys	Val	Arg	Cys	Ala	Thr	Glu	Leu	Asp
145					150					155					160
Arg	His	Lys	Ile	Leu	Leu	His	Leu	Gly	Phe	Ile	Met	Ala	Ser	Leu	Leu
			165						170					175	
Phe	Leu	Val	Val	Asn	Leu	Thr	Cys	Ala	Met	Leu	Val	His	Gly	Asp	Val
			180					185					190		
Pro	Glu	Asn	Gln	Leu	Lys	Trp	Thr	Val	Phe	Val	Arg	Ala	Leu	Ile	Asn
		195				200						205			
Asp	Ser	Leu	Phe	Ile	Leu	Cys	Ala	Ile	Ser	Leu	Val	Cys	Tyr	Ile	Cys
	210					215					220				
Lys	Ile	Thr	Lys	Met	Ser	Ser	Ala	Asn	Val	Tyr	Leu	Glu	Ser	Lys	Gly
225					230					235					240
Met	Ser	Leu	Cys	Gln	Thr	Val	Ile	Val	Gly	Ser	Val	Val	Ile	Leu	Leu
				245					250					255	

Tyr Ser Ser Arg Ala Cys Tyr Asn Leu Val Val Val Thr Ile Ser Gln
 260 265 270
 Asp Thr Leu Glu Ser Pro Phe Asn Tyr Gly Trp Asp Asn Leu Ser Asp
 275 280 285
 Lys Ala His Val Glu Asp Ile Ser Gly Glu Glu Tyr Ile Val Phe Gly
 290 295 300
 Met Val Leu Phe Leu Trp Glu His Val Pro Ala Trp Ser Val Val Leu
 305 310 315 320
 Phe Phe Arg Ala Gln Arg Leu Asn Gln Asn Leu Ala Pro Ala Gly Met
 325 330 335
 Ile Asn Ser His Ser Tyr Ser Ser Arg Ala Tyr Phe Phe Asp Asn Pro
 340 345 350
 Arg Arg Tyr Asp Ser Asp Asp Asp Leu Pro Arg Leu Gly Ser Ser Arg
 355 360 365
 Glu Gly Ser Leu Pro Asn Ser Gln Ser Leu Gly Trp Tyr Gly Thr Met
 370 375 380
 Thr Gly Cys Gly Ser Ser Ser Tyr Thr Val Thr Pro His Leu Asn Gly
 385 390 395 400
 Pro Met Thr Asp Thr Ala Pro Leu Leu Phe Thr Cys Ser Asn Leu Asp
 405 410 415
 Leu Asn Asn His His Ser Leu Tyr Val Thr Pro Gln Asn
 420 425

<210> 392
 <211> 1584
 <212> DNA
 <213> Homo sapiens

<400> 392
 ggaagactgg agccttttgcg gcggcgctgc ccctcccctg gtccccgcga gctcggaggg 60
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 ggtggtcgtg tgtggccagg cgtctgtggg caaaacttca atcctggagc agcttctgta 180
 tgggaaccat gtagtgggtt cggagatgat cgagacgcag gaggacatct acgtgggctc 240
 cattgagaca gaccgggggg tgcgagagca ggtgcgtttc tatgacaccc gggggctccg 300
 agatggggcc gaactgcccc gacactgctt ctcttgact gatggctacg tcctgggtcta 360
 tagcacagat agcagagagt cttttcagcg tgtggagctg ctcaagaagg agattgacaa 420
 atccaaggac aagaaggagg tcaccatcgt ggtccttggc aacaagtgtg acttacagga 480
 gcagcggcgt gtagaccag atgtggctca gcactgggcc aagtcagaga aggtgaagct 540
 gtgggaggtg tcagtggcgg accggcgctc cctcctggag ccctttgtct acttggccag 600
 caagatgacg caaccccaga gcaagtctgc cttccccctc agccggaaga acaagggcag 660
 cggctccttg gatggctgaa gagctgccgt tcctctttca cgatcccagc cccatttcag 720
 tgtctggggc tctggtagat gtgttgaggg caaagtagag gacaagctgt ctttcccagt 780

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<210> 393
<211> 191
<212> PRT
<213> Homo sapiens

<400> 393
Met Gly Lys Ser Cys Lys Val Val Val Cys Gly Gln Ala Ser Val Gly
      5              10              15
Lys Thr Ser Ile Leu Glu Gln Leu Leu Tyr Gly Asn His Val Val Gly
      20              25              30
Ser Glu Met Ile Glu Thr Gln Glu Asp Ile Tyr Val Gly Ser Ile Glu
      35              40              45
Thr Asp Arg Gly Val Arg Glu Gln Val Arg Phe Tyr Asp Thr Arg Gly
      50              55              60
Leu Arg Asp Gly Ala Glu Leu Pro Arg His Cys Phe Ser Cys Thr Asp
      65              70              75              80
Gly Tyr Val Leu Val Tyr Ser Thr Asp Ser Arg Glu Ser Phe Gln Arg
      85              90              95
Val Glu Leu Leu Lys Lys Glu Ile Asp Lys Ser Lys Asp Lys Lys Glu
      100              105              110
Val Thr Ile Val Val Leu Gly Asn Lys Cys Asp Leu Gln Glu Gln Arg
      115              120              125
Arg Val Asp Pro Asp Val Ala Gln His Trp Ala Lys Ser Glu Lys Val
      130              135              140
Lys Leu Trp Glu Val Ser Val Ala Asp Arg Arg Ser Leu Leu Glu Pro
      145              150              155              160
Phe Val Tyr Leu Ala Ser Lys Met Thr Gln Pro Gln Ser Lys Ser Ala
      165              170              175

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Phe Pro Leu Ser Arg Lys Asn Lys Gly Ser Gly Ser Leu Asp Gly
 180 185 190

<210> 394
 <211> 1937
 <212> DNA
 <213> Homo sapiens

<400> 394
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 cagtgtctcg gctcagccag aacacaaagc gtgaatccgg aagaaaagtt caatctggaa 120
 acatcaatgc tgccaagact attgcagata tcatccgaac atgttttgga cccaagtcca 180
 tgatgaagat gcttttggac ccaatgggag gcattgtgat gaccaatgat ggcaatgcca 240
 ttcttcgaga gattcaagtc cagcatccag cggccaagtc catgatcgaa attagccgga 300
 cccaggatga agaggttgga gatgggacca catcagtaat tattcttgca ggggaaatgc 360
 tgtctgtagc tgagcacttc ctggagcagc agatgcaccc aacagtgggtg atcagtgcctt 420
 accgcaaggc attggatgat atgatcagca ccctaaagaa aataagtatc ccagtgcaca 480
 tcagtgcacg tgatatgatg ctgaacatca tcaacagctc tattactacc aaagccatca 540
 gtcggtggtc atctttggct tgcaacattg ccctggatgc tgtcaagatg gtacagtttg 600
 aggagaatgg tcggaaagag attgacataa aaaaatatgc aagagtggaa aagatacctg 660
 gaggcacatc tgaagactcc tgtgtcttgc gtggagtcac gattaacaag gatgtgaccc 720
 atccacgtat gcggcgctat atcaagaacc ctgcgattgt gctgctggat tcttctctgg 780
 aatacaagaa aggagaaagc cagactgaca ttgagattac acgagaggag gacttcaccc 840
 gaattctcca gatggaggaa gagtacatcc agcagctctg tgaggacatt atccaactga 900
 agcccgatgt ggtcatcact gaaaagggca tctcagattt agctcagcac taccttatgc 960
 gggccaatat cacagccatc cgcagagtcg ggaagacaga caataatcgc attgctagag 1020
 cctgtggggc ccgatatgac agccgaccag aggaactgag agaagatgat gttggaacag 1080
 gagcaggcct gttggaaatc aagaaaattg gagatgaata ctttactttc atcactgact 1140
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 ccaaggccat gactggtgtg gaacaatggc catacagggc tgttgcccag gccctagagg 1380
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 ctttgggtgga catgaaggaa ctgggcatac gggagccatt ggctgtgaag ctgcagactt 1560
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 cagagtgcc aagacactgt ggacgtcttt gttcagaagg gatcagggtt gggggcagcc 1800
 cccagtcctt ttctgtccca gctcagtttt ccaaaagaca ctgacatgta attcttctct 1860
 attgtaaggt ttccatttag tttgcttccg atgattaaat ctaagtcatt tgaaaaaaaa 1920
 aaaaaaaaaa actcgag 1937

<210> 395
 <211> 1675
 <212> DNA
 <213> Homo sapiens

<400> 395
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 tgtgactgag gtgaccatca tagaaaagcc tcctgctgaa cgtcatatga tttcttctct 180
 ggaacaaaag aataactgtg tgatgcctga agatgtgaag aacttttacc tgatgaccaa 240
 tggcttccac atgacatgga gtgtgaagct ggatgagcac atcattccac tgggaagcat 300

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ggcaattaac agcatctcaa aactgactca gctcaccag tcttccatgt attcacttcc 360
taatgcaccc actctggcag acctggagga cgatacacat gaagccagt atgatcagcc 420
agagaagcct cactttgact ctgcagagt gatatttgag ctggattcat gcaatggcag 480
tggaagagt tgccttgtct acaaaagtgg gaaaccagca ttagcagaag aactgagat 540
ctggttcctg gacagagcgt tatactggca ttttctcaca gacacctta ctgcctatta 600
ccgcctgctc atcaccacc tgggcctgcc ccagtggcaa tatgccttca ccagctatgg 660
cattagccca caggccaagc aatgggttcag catgtataaa cctatcacct acaacacaaa 720
cctgctcaca gaagagaccg actcctttgt gaataagcta gatcccagca aagtgtttta 780
gagcaagaac aagatcgtaa tccccaaaaa gaaagggcct gtgcagcctg caggtggcca 840
gaaagggccc tcaggaccct ccggtccctc cacttccctc acttctaaat cctcctctgg 900
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caaccctcaa tcccttagca ctgattgatt agagagggtc cccaaagaaa ccactggttt 1260
tgacctatga agcattagaa ctgcattgtt cattcaggag ccactagtca catatgacta 1320
tttaaattta aagtaaattg tatgaaaaat tcatttcttc aattgcatta gccacatttt 1380
gagtattcat gtggctggtg gattctgtat tagcaciaag atatggaaca tttccatcac 1440
cacagaaagt tctgttggaac agcactgcat tagaatattt tcatactgct cttcctcaat 1500
taatttttgt tgtaaatgtt gatgtcttca ttggatgggt cataatgttc catgaaacct 1560
ctcaagtaca caattgtatg ttctttgtat cccttaccac aaatatctcg ctctgctcat 1620
ttcttttgca gcttcctata aagtttgtct tcctcatcaa aaaaaaaaaa aaaaa 1675

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<210> 396

<211> 559

<212> PRT

<213> Homo sapiens

<400> 396

Gly Ser Pro Ser Ser Gly Tyr Pro Ala Leu His Arg Val Ala Met Met
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Gly His Arg Pro Val Leu Val Leu Ser Gln Asn Thr Lys Arg Glu Ser
20 25 30

Gly Arg Lys Val Gln Ser Gly Asn Ile Asn Ala Ala Lys Thr Ile Ala
35 40 45

Asp Ile Ile Arg Thr Cys Leu Gly Pro Lys Ser Met Met Lys Met Leu
50 55 60

Leu Asp Pro Met Gly Gly Ile Val Met Thr Asn Asp Gly Asn Ala Ile
65 70 75 80

Leu Arg Glu Ile Gln Val Gln His Pro Ala Ala Lys Ser Met Ile Glu
85 90 95

Ile Ser Arg Thr Gln Asp Glu Glu Val Gly Asp Gly Thr Thr Ser Val
100 105 110

Ile Ile Leu Ala Gly Glu Met Leu Ser Val Ala Glu His Phe Leu Glu
115 120 125

Gln Gln Met His Pro Thr Val Val Ile Ser Ala Tyr Arg Lys Ala Leu
 130 135 140
 Asp Asp Met Ile Ser Thr Leu Lys Lys Ile Ser Ile Pro Val Asp Ile
 145 150 155 160
 Ser Asp Ser Asp Met Met Leu Asn Ile Ile Asn Ser Ser Ile Thr Thr
 165 170 175
 Lys Ala Ile Ser Arg Trp Ser Ser Leu Ala Cys Asn Ile Ala Leu Asp
 180 185 190
 Ala Val Lys Met Val Gln Phe Glu Glu Asn Gly Arg Lys Glu Ile Asp
 195 200 205
 Ile Lys Lys Tyr Ala Arg Val Glu Lys Ile Pro Gly Gly Ile Ile Glu
 210 215 220
 Asp Ser Cys Val Leu Arg Gly Val Met Ile Asn Lys Asp Val Thr His
 225 230 235 240
 Pro Arg Met Arg Arg Tyr Ile Lys Asn Pro Arg Ile Val Leu Leu Asp
 245 250 255
 Ser Ser Leu Glu Tyr Lys Lys Gly Glu Ser Gln Thr Asp Ile Glu Ile
 260 265 270
 Thr Arg Glu Glu Asp Phe Thr Arg Ile Leu Gln Met Glu Glu Glu Tyr
 275 280 285
 Ile Gln Gln Leu Cys Glu Asp Ile Ile Gln Leu Lys Pro Asp Val Val
 290 295 300
 Ile Thr Glu Lys Gly Ile Ser Asp Leu Ala Gln His Tyr Leu Met Arg
 305 310 315 320
 Ala Asn Ile Thr Ala Ile Arg Arg Val Arg Lys Thr Asp Asn Asn Arg
 325 330 335
 Ile Ala Arg Ala Cys Gly Ala Arg Ile Val Ser Arg Pro Glu Glu Leu
 340 345 350
 Arg Glu Asp Asp Val Gly Thr Gly Ala Gly Leu Leu Glu Ile Lys Lys
 355 360 365
 Ile Gly Asp Glu Tyr Phe Thr Phe Ile Thr Asp Cys Lys Asp Pro Lys
 370 375 380
 Ala Cys Thr Ile Leu Leu Arg Gly Ala Ser Lys Glu Ile Leu Ser Glu
 385 390 395 400
 Val Glu Arg Asn Leu Gln Asp Ala Met Gln Val Cys Arg Asn Val Leu
 405 410 415

Leu Gly Ser Met Ala Ile Asn Ser Ile Ser Lys Leu Thr Gln Leu Thr
100 105 110

Gln Ser Ser Met Tyr Ser Leu Pro Asn Ala Pro Thr Leu Ala Asp Leu
115 120 125

Glu Asp Asp Thr His Glu Ala Ser Asp Asp Gln Pro Glu Lys Pro His
130 135 140

Phe Asp Ser Arg Ser Val Ile Phe Glu Leu Asp Ser Cys Asn Gly Ser
145 150 155 160

Gly Lys Val Cys Leu Val Tyr Lys Ser Gly Lys Pro Ala Leu Ala Glu
165 170 175

Asp Thr Glu Ile Trp Phe Leu Asp Arg Ala Leu Tyr Trp His Phe Leu
180 185 190

Thr Asp Thr Phe Thr Ala Tyr Tyr Arg Leu Leu Ile Thr His Leu Gly
195 200 205

Leu Pro Gln Trp Gln Tyr Ala Phe Thr Ser Tyr Gly Ile Ser Pro Gln
210 215 220

Ala Lys Gln Trp Phe Ser Met Tyr Lys Pro Ile Thr Tyr Asn Thr Asn
225 230 235 240

Leu Leu Thr Glu Glu Thr Asp Ser Phe Val Asn Lys Leu Asp Pro Ser
245 250 255

Lys Val Phe Lys Ser Lys Asn Lys Ile Val Ile Pro Lys Lys Lys Gly
260 265 270

Pro Val Gln Pro Ala Gly Gly Gln Lys Gly Pro Ser Gly Pro Ser Gly
275 280 285

Pro Ser Thr Ser Ser Thr Ser Lys Ser Ser Ser Gly Ser Gly Asn Pro
290 295 300

Thr Arg Lys
305

<210> 398

<211> 416

<212> DNA

<213> Homo sapiens

<400> 398

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ccgactttga ggggcctatg cccagtgcgc cccagaagc tgaaagtcct cttgcctcaa 180
ccagcaagga ggagaaggat gaatgtgctc tcatttccac tagcatagca gaagaatgtg 240
aggcttctgt ttccggtgta gttgttgaaa gtgaaaatga gcgagctggc acagtcatgg 300

aagaaaaaga cgggagtggc atcatctcta cgagctcggg ggaagactgt gagggcccag 360
tgtccagtgc tgtccctcaa gaggaaggcg acccctcagt cacaccagcg gaagag 416

<210> 399
<211> 259
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(259)
<223> n = A,T,C or G

<400> 399
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aaaagttcag ccccgcgggg cctgtgctgt ncatccgggt ctgccgngat atgatacccc 120
gccgctccct gggctatgcc tacgncaact tccanacaacc ggccgacgct gatcgggctt 180
tggacaccat gaactttgat gtgattnagg gaaanccaat ccttatcntg tnnnaatcat 240
aggnatcctt ctttgacaa 259

<210> 400
<211> 410
<212> DNA
<213> Homo sapiens

<400> 400
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agttaccatc acaccccggg aggagccgca gctgccgcag ccggccccag tcaccatcac 120
cgcaaccatg agcagcggag ccgagaccca gcagccgccc gccgcccccc cccgccgccc 180
ccgccctcag cgcgcgagc accaagcccc gcactacggg cagcggcgca gggagcgggtg 240
gcccggggcg cctcacatcg gcggcgccctg ccggcgggga caagaaggtc atcgcaacga 300
aggtttttggg aacagtaaaa tggttcaatg taaggaacgg atatggtttc atcaacagga 360
atgacaccaa ggaagatgta tttgtacacc agactgccat aaagaagaat 410

<210> 401
<211> 433
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(433)
<223> n = A,T,C or G

<400> 401
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ccacggagcc tccggggctg ccggcacagt cttcactacc gtagaagacc ttggctccaa 120
gatactcctc acctgctcct tgaatgacag cgccacagag gtcacagggc accgctggct 180
gaagggggggc gtgggtgctga aggaggacgc gctgcccggc cagaaaacgg agttcaaggt 240
ggactccgac gaccagtggg gagagtactc ctgcgtcttc ctccccgagc ccatgggcac 300
ggccaacatc cagctccacg ggccctcccag agtgaaggcc gtgaagtcgt cagaacacat 360
caacgagggg gagacggcca tgctgggtctg caagtcagag tccgtgccac ctgtcactga 420
ctgggcctgg tac 433

<210> 402
 <211> 434
 <212> DNA
 <213> Homo sapiens

<400> 402
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 gcctgtcgct tgtcttctat tcacccatggc ttcttctgat atccagggtga aagaactgga 120
 gaagcgtgcc tcaggccagg cttttgagct gattctcage cctcgggtcaa aaggatctgt 180
 tccagaattc cccctttccc ctccaaagaa gaaggatctt tccctggagg aaattcagaa 240
 gaaattagaa gctgcagaag aaagacgcaa gtcccatgaa gctgaggtct tgaagcagct 300
 ggctgagaaa cgagagcacg agaaagaagt gcttcagaag gcaatagaag agaacaacaa 360
 cttcagtaaa atggcagaag agaaactgac ccacaaaatg gaagctaata aagagaaccg 420
 agaggcacia atgg 434

<210> 403
 <211> 435
 <212> DNA
 <213> Homo sapiens

<400> 403
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 gagctctttt aagccaatgg gatttgaagt atcatttctg aagtttcttg aggagtctgc 120
 agtgaagcag aagaaaaata ctgacaaaga ccatccgaat actggaaaca aaaaaggatc 180
 ccattcaaat tcaagaaaaa atattgataa gactgctgtg actagtggaa atcatgtatg 240
 tccttgtaaa gaaagcgaaa cgtttgtaca gtttgccaat ccatcacagc ttcagtgcag 300
 tgataatgta aaaattgttt tagacaagaa tcttaaagat tgcactgagc ttgtcttaaa 360
 gcaacttcag gaaatgaaac ctaccgtcag tctgaaaaaa cttgaagtac attcaaatga 420
 tccagatatg tctgt 435

<210> 404
 <211> 416
 <212> DNA
 <213> Homo sapiens

<400> 404
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<212> DNA

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<213> Homo sapiens

<400> 421

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Phe Asp Ile Ile Ala Tyr Thr Asp Pro Glu Leu Asp Met Gly Asp Lys						
		1810		1815		1820
Lys Ser Met Phe Asn Glu Glu Leu Asp Leu Pro Ile Asp Asp Lys Leu						
		1825		1830		1835
				1835		1840
Asp Asn Gln Cys Val Ser Val Glu Pro Lys Lys Lys Glu Gln Glu Asn						
		1845		1850		1855
Lys Thr Leu Val Leu Ser Asp Lys His Ser Pro Gln Lys Lys Ser Thr						
		1860		1865		1870
Val Thr Asn Glu Val Lys Thr Glu Val Leu Ser Pro Asn Ser Lys Val						
		1875		1880		1885
Glu Ser Lys Cys Glu Thr Glu Lys Asn Asp Glu Asn Lys Asp Asn Val						
		1890		1895		1900
Asp Thr Pro Cys Ser Gln Ala Ser Ala His Ser Asp Leu Asn Asp Gly						
		1905		1910		1915
				1915		1920
Glu Lys Thr Ser Leu His Pro Cys Asp Pro Asp Leu Phe Glu Lys Arg						
		1925		1930		1935
Thr Asn Arg Glu Thr Ala Gly Pro Ser Ala Asn Val Ile Gln Ala Ser						
		1940		1945		1950
Thr Gln Leu Pro Ala Gln Asp Val Ile Asn Ser Cys Gly Ile Thr Gly						
		1955		1960		1965
Ser Thr Pro Val Leu Ser Ser Leu Leu Ala Asn Glu Lys Ser Asp Asn						
		1970		1975		1980
Ser Asp Ile Arg Pro Ser Gly Ser Pro Pro Pro Pro Thr Leu Pro Ala						
		1985		1990		1995
				1995		2000
Ser Pro Ser Asn His Val Ser Ser Leu Pro Pro Phe Ile Ala Pro Pro						
		2005		2010		2015
Gly Arg Val Leu Asp Asn Ala Met Asn Ser Asn Val Thr Val Val Ser						
		2020		2025		2030
Arg Val Asn His Val Phe Ser Gln Gly Val Gln Val Asn Pro Gly Leu						

2035	2040	2045
Ile Pro Gly Gln Ser Thr Val Asn His Ser Leu Gly Thr Gly Lys Pro 2050	2055	2060
Ala Thr Gln Thr Gly Pro Gln Thr Ser Gln Ser Gly Thr Ser Ser Met 2065	2070	2075 2080
Ser Gly Pro Gln Gln Leu Met Ile Pro Gln Thr Leu Ala Gln Gln Asn 2085	2090	2095
Arg Glu Arg Pro Leu Leu Leu Glu Glu Gln Pro Leu Leu Leu Gln Asp 2100	2105	2110
Leu Leu Asp Gln Glu Arg Gln Glu Gln Gln Gln Arg Gln Met Gln 2115	2120	2125
Ala Met Ile Arg Gln Arg Ser Glu Pro Phe Phe Pro Asn Ile Asp Phe 2130	2135	2140
Asp Ala Ile Thr Asp Pro Ile Met Lys Ala Lys Met Val Ala Leu Lys 2145	2150	2155 2160
Gly Ile Asn Lys Val Met Ala Gln Asn Asn Leu Gly Met Pro Pro Met 2165	2170	2175
Val Met Ser Arg Phe Pro Phe Met Gly Gln Val Val Thr Gly Thr Gln 2180	2185	2190
Asn Ser Glu Gly Gln Asn Leu Gly Pro Gln Ala Ile Pro Gln Asp Gly 2195	2200	2205
Ser Ile Thr His Gln Ile Ser Arg Pro Asn Pro Pro Asn Phe Gly Pro 2210	2215	2220
Gly Phe Val Asn Asp Ser Gln Arg Lys Gln Tyr Glu Glu Trp Leu Gln 2225	2230	2235 2240
Glu Thr Gln Gln Leu Leu Gln Met Gln Gln Lys Tyr Leu Glu Glu Gln 2245	2250	2255
Ile Gly Ala His Arg Lys Ser Lys Lys Ala Leu Ser Ala Lys Gln Arg 2260	2265	2270
Thr Ala Lys Lys Ala Gly Arg Glu Phe Pro Glu Glu Asp Ala Glu Gln 2275	2280	2285
Leu Lys His Val Thr Glu Gln Gln Ser Met Val Gln Lys Gln Leu Glu 2290	2295	2300
Gln Ile Arg Lys Gln Gln Lys Glu His Ala Glu Leu Ile Glu Asp Tyr 2305	2310	2315 2320
Arg Ile Lys Gln Gln Gln Gln Cys Ala Met Ala Pro Pro Thr Met Met		

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 Gln Gln His Thr Thr Val Ile Ser Gly His Thr Ser Pro Val Arg Met
 2370 2375 2380
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 Ser Phe Gln Glu Arg Glu Arg Lys Glu Arg Leu Arg Glu Gln Gln Glu
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 Ser Ser Ser Arg Thr Ser Val Ser Gln Ile Pro Phe Tyr Ser Ser Asp
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 Gly Lys Lys Lys Arg Thr Arg Lys Lys Lys Arg Asp Asp Asp Ala Glu
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 Ser Thr Lys Ala Pro Ser Thr Pro His Ser Asp Ile Thr Ala Pro Pro
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 Thr Pro Gly Ile Ser Glu Thr Thr Ser Thr Pro Ala Val Ser Thr Pro
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 Thr Tyr Ala Asn Ser Glu Val Asp Lys Leu Ser Met Glu Thr Pro Ala
 2755 2760 2765
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 2770 2775 2780
 Gly Gln Glu Glu Pro Lys Leu Glu Glu Gln Asn Gly Ser Lys Val Glu
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 Lys His Leu Leu Lys Asn Lys Lys Ser Ser Ser Leu Leu Asn Gln Lys
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Thr	Glu	Pro	Gly	Thr	Leu	Tyr	Phe	Ala	Ser	Pro	Phe	Gly	Pro	Ser	Pro	
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Asn	Gly	Pro	Arg	Ser	Gly	Leu	Ile	Ser	Val	Ala	Ile	Thr	Leu	His	Pro	

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 3220 3225 3230
 Val Pro Ser Met Gly Leu Val Ser Ser His Arg Ile Asn Pro Gly Leu
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Glu Thr Gln Ala Gly Ala Leu Ile Asn Val Glu Leu Ala Leu Arg Arg		
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Gly Cys His Arg Phe Arg Cys Thr Asn Ile Tyr His Phe Thr Cys Ala		
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Ile Lys Ala Gln Cys Met Phe Phe Lys Asp Lys Thr Met Leu Cys Pro		
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Met His Lys Pro Lys Gly Ile His Glu Gln Glu Leu Ser Tyr Phe Ala		
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Leu Ile Phe His Thr Ile Gly Gln Leu Leu Pro Gln Gln Met Gln Ala		
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Glu Gln Gly His Glu Asp Leu Val Leu Ser Asp Ile Ser Pro Lys Gly		
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Val Trp Asp Lys Ile Leu Glu Pro Val Ala Cys Val Arg Lys Lys Ser		
3745	3750	3755 3760
Glu Met Leu Gln Leu Phe Pro Ala Tyr Leu Lys Gly Glu Asp Leu Phe		

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 Pro Lys Met Ser Ala His Val Lys Arg Pro His Thr Leu Asn Ser Thr
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 Pro Tyr Ser Lys Gln Phe Val His Ser Lys Ser Ser Gln Tyr Arg Lys
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 Thr Phe Glu Arg Gly His Lys Ile Ile Ile Ser Ser Ser Arg Arg Ile
 3970 3975 3980
 Gln Lys Gly Glu Glu Leu Cys Tyr Asp Tyr Lys Phe Asp Phe Glu Asp
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<211> 174

<212> PRT

<400> 426

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Val Thr Ala Pro Leu Pro Gln Ala Ala His Cys Val Leu Ala Gln Asp
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Pro Glu Asn Gln Ala Leu Ala Arg Phe Tyr Cys Tyr Thr Glu Arg Thr
50 55 60

Ile Ala Lys Arg Leu Val Leu Arg Arg Asp Pro Ser Val Lys Arg Thr
65 70 75 80

Leu Cys Arg Gly Cys Ser Ser Leu Leu Val Pro Gly Leu Thr Cys Thr
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His Arg Gln Arg Arg Cys Arg Gly Gln Arg Trp Thr Val Gln Thr Cys
100 105 110

Leu Thr Cys Gln Arg Ser Gln Arg Phe Leu Asn Asp Pro Gly His Leu
115 120 125

Leu Trp Gly Asp Arg Pro Glu Ala Gln Leu Gly Ser Gln Ala Asp Ser
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Leu Pro Glu Glu Lys Met Gln Thr Gln Gly Ser Ser Asn Gln
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<210> 427

<211> 184

<212> PRT

<213> Homo sapiens

<400> 427

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Leu Tyr Leu Gly Ile Arg Gln Val Ser Lys Pro Leu Ala Asn Arg Ile
20 25 30

Lys Glu Ala Ala Arg Arg Ser Glu Phe Phe Lys Thr Tyr Ile Cys Leu
35 40 45

Pro Pro Ala Gln Leu Tyr His Trp Val Glu Met Arg Thr Lys Met Arg
50 55 60

Ile Met Gly Phe Arg Gly Thr Val Ile Lys Pro Leu Asn Glu Glu Ala
 65 70 75 80
 Ala Ala Glu Leu Gly Ala Glu Leu Leu Gly Glu Ala Thr Ile Phe Ile
 85 90 95
 Val Gly Gly Gly Cys Leu Val Leu Glu Tyr Trp Arg His Gln Ala Gln
 100 105 110
 Gln Arg His Lys Glu Glu Glu Gln Arg Ala Ala Trp Asn Ala Leu Arg
 115 120 125
 Asp Glu Val Gly His Leu Ala Leu Ala Leu Glu Ala Leu Gln Ala Gln
 130 135 140
 Val Gln Ala Ala Pro Pro Gln Gly Ala Leu Glu Glu Leu Arg Thr Glu
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 His Ala Val Pro Ala Ser Lys Lys
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<210> 428
 <211> 6476
 <212> DNA
 <213> Homo sapiens

<400> 428
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<211> 732

<212> DNA

<213> Homo sapiens

<400> 429

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<210> 431
<211> 640
<212> DNA
<213> Homo sapiens

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<210> 432
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<212> DNA
<213> Homo sapiens

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<210> 433
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 <212> DNA
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<210> 434
 <211> 1702
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Pro Tyr Val Gln Asp Ile His Ser Val Gly Ser Leu Cys Lys Leu Tyr
 50 55 60
 Phe Arg Glu Leu Pro Asn Pro Leu Leu Thr Tyr Gln Leu Tyr Glu Lys
 65 70 75 80
 Phe Ser Asp Ala Val Ser Ala Ala Thr Asp Glu Glu Arg Leu Ile Lys
 85 90 95
 Ile His Asp Val Ile Gln Gln Leu Pro Pro Pro His Tyr Arg Thr Leu
 100 105 110
 Glu Phe Leu Met Arg His Leu Ser Leu Leu Ala Asp Tyr Cys Ser Ile
 115 120 125
 Thr Asn Met His Ala Lys Asn Leu Ala Ile Val Trp Ala Pro Asn Leu
 130 135 140
 Leu Arg Ser Lys Gln Ile Glu Ser Ala Cys Phe Ser Gly Thr Ala Ala
 145 150 155 160
 Phe Met Glu Val Arg Ile Gln Ser Val Val Val Glu Phe Ile Leu Asn
 165 170 175
 His Val Asp Val Leu Phe Ser Gly Arg Ile Ser Met Ala Met Gln Glu
 180 185 190
 Gly Ala Ala Ser Leu Ser Arg Pro Lys Ser Leu Leu Val Ser Ser Pro
 195 200 205
 Ser Thr Lys Leu Leu Thr Leu Glu Glu Ala Gln Ala Arg Thr Gln Ala
 210 215 220
 Gln Val Asn Ser Pro Ile Val Thr Glu Asn Lys Tyr Ile Glu Val Gly
 225 230 235 240
 Glu Gly Pro Ala Ala Leu Gln Gly Lys Phe His Thr Ile Ile Glu Phe
 245 250 255
 Pro Leu Glu Arg Lys Arg Pro Gln Asn Lys Met Lys Lys Ser Pro Val
 260 265 270
 Gly Ser Trp Arg Ser Phe Phe Asn Leu Gly Lys Ser Ser Ser Val Ser
 275 280 285
 Lys Arg Lys Leu Gln Arg Asn Glu Ser Glu Pro Ser Glu Met Lys Ala
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Ser	Glu	Glu	Ser	Leu 325	Thr	Ser	Leu	His	Ala 330	Val	Asp	Gly	Asp	Ser 335	Lys
Leu	Phe	Arg	Pro 340	Arg	Arg	Pro	Arg	Ser 345	Ser	Ser	Asp	Ala	Leu 350	Ser	Ala
Ser	Phe	Asn 355	Gly	Glu	Met	Leu	Gly 360	Asn	Arg	Cys	Asn 365	Ser	Tyr	Asp	Asn
Leu 370	Pro	His	Asp	Asn	Glu	Ser 375	Glu	Glu	Glu	Gly 380	Gly	Leu	Leu	His	Ile
Pro 385	Ala	Leu	Met	Ser	Pro 390	His	Ser	Ala	Glu	Asp 395	Val	Asp	Leu	Ser	Pro 400
Pro	Asp	Ile	Gly 405	Val	Ala	Ser	Leu	Asp	Phe 410	Asp	Pro	Met	Ser	Phe 415	Gln
Cys	Ser	Pro 420	Pro	Lys	Ala	Glu	Ser 425	Glu	Cys	Leu	Glu	Ser	Gly 430	Ala	Ser
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Lys 450	Asp	Ala	Glu	Thr	Gly	Ser 455	Ser	Gln	Cys	Gln 460	Thr	Pro	Gly	Ser	Thr
Ala 465	Ser	Ser	Glu	Pro	Val 470	Ser	Pro	Leu	Gln	Glu 475	Lys	Leu	Ser	Pro	Phe 480
Phe	Thr	Leu	Asp 485	Leu	Ser	Pro	Thr	Glu	Asp 490	Lys	Ser	Ser	Lys	Pro 495	Ser
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 625 630 635 640
 Ser Val Ser Leu Ile Pro Pro Pro Pro Pro Lys Asn Val Ala Arg
 645 650 655
 Met Leu Ala Leu Ala Leu Ala Glu Ser Ala Gln Gln Ala Ser Thr Gln
 660 665 670
 Ser Leu Lys Arg Pro Gly Thr Ser Gln Ala Gly Tyr Thr Asn Tyr Gly
 675 680 685
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 690 695 700
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 Pro Leu Asp Ser Glu Lys Ser Asp Asp His Val Ser Phe Pro Glu Asp
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 805 810 815
 Gln Ser Pro Pro Arg Phe Tyr Ser Gly Asp Gln Pro Pro Ser Tyr Leu
 820 825 830
 Gly Ala Ser Val Asp Lys Leu His His Pro Leu Glu Phe Ala Asp Lys
 835 840 845
 Ser Pro Thr Pro Pro Asn Leu Pro Ser Asp Lys Ile Tyr Pro Pro Ser
 850 855 860
 Gly Ser Pro Glu Glu Asn Thr Ser Thr Ala Thr Met Thr Tyr Met Thr
 865 870 875 880

Thr Thr Pro Ala Thr Ala Gln Met Ser Thr Lys Glu Ala Ser Trp Asp
 885 890 895
 Val Ala Glu Gln Pro Thr Thr Ala Asp Phe Ala Ala Ala Thr Leu Gln
 900 905 910
 Arg Thr His Arg Thr Asn Arg Pro Leu Pro Pro Pro Pro Ser Gln Arg
 915 920 925
 Ser Ala Glu Gln Pro Pro Val Val Gly Gln Val Gln Ala Ala Thr Asn
 930 935 940
 Ile Gly Leu Asn Asn Ser His Lys Val Gln Gly Val Val Pro Val Pro
 945 950 955 960
 Glu Arg Pro Pro Glu Pro Arg Ala Met Asp Asp Pro Ala Ser Ala Phe
 965 970 975
 Ile Ser Asp Ser Gly Ala Ala Ala Ala Gln Cys Pro Met Ala Thr Ala
 980 985 990
 Val Gln Pro Gly Leu Pro Glu Lys Val Arg Asp Gly Ala Arg Val Pro
 995 1000 1005
 Leu Leu His Leu Arg Ala Glu Ser Val Pro Ala His Pro Cys Gly Phe
 1010 1015 1020
 Pro Ala Pro Leu Pro Pro Thr Arg Met Met Glu Ser Lys Met Ile Ala
 1025 1030 1035 1040
 Ala Ile His Ser Ser Ser Ala Asp Ala Thr Ser Ser Ser Asn Tyr His
 1045 1050 1055
 Ser Phe Val Thr Ala Ser Ser Thr Ser Val Asp Asp Ala Leu Pro Leu
 1060 1065 1070
 Pro Leu Pro Val Pro Gln Pro Lys His Ala Ser Gln Lys Thr Val Tyr
 1075 1080 1085
 Ser Ser Phe Ala Arg Pro Asp Val Thr Thr Glu Pro Phe Gly Pro Asp
 1090 1095 1100
 Asn Cys Leu His Phe Asn Met Thr Pro Asn Cys Gln Tyr Arg Pro Gln
 1105 1110 1115 1120
 Ser Val Pro Pro His His Asn Lys Leu Glu Gln His Gln Val Tyr Gly
 1125 1130 1135
 Ala Arg Ser Glu Pro Pro Ala Ser Met Gly Leu Arg Tyr Asn Thr Tyr
 1140 1145 1150
 Val Ala Pro Gly Arg Asn Ala Ser Gly His His Ser Lys Pro Cys Ser
 1155 1160 1165

Arg	Val	Glu	Tyr	Val	Ser	Ser	Leu	Ser	Ser	Ser	Val	Arg	Asn	Thr	Cys	
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Tyr	Pro	Glu	Asp	Ile	Pro	Pro	Tyr	Pro	Thr	Ile	Arg	Arg	Val	Gln	Ser	
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Leu	His	Ala	Pro	Pro	Ser	Ser	Met	Ile	Arg	Ser	Val	Pro	Ile	Ser	Arg	
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Thr	Glu	Val	Pro	Pro	Asp	Asp	Glu	Pro	Ala	Tyr	Cys	Pro	Arg	Pro	Leu	
			1220					1225					1230			
Tyr	Gln	Tyr	Lys	Pro	Tyr	Gln	Ser	Ser	Gln	Ala	Arg	Ser	Asp	Tyr	His	
	1235						1240					1245				
Val	Thr	Gln	Leu	Gln	Pro	Tyr	Phe	Glu	Asn	Gly	Arg	Val	His	Tyr	Arg	
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Tyr	Ser	Pro	Tyr	Ser	Ser	Ser	Ser	Ser	Ser	Tyr	Tyr	Ser	Pro	Asp	Gly	
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Ala	Leu	Cys	Asp	Val	Asp	Ala	Tyr	Gly	Thr	Val	Gln	Leu	Arg	Pro	Leu	
				1285					1290						1295	
His	Arg	Leu	Pro	Asn	Arg	Asp	Phe	Ala	Phe	Tyr	Asn	Pro	Arg	Leu	Gln	
			1300					1305					1310			
Gly	Lys	Ser	Leu	Tyr	Ser	Tyr	Ala	Gly	Leu	Ala	Pro	Arg	Pro	Arg	Ala	
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Asn	Val	Thr	Gly	Tyr	Phe	Ser	Pro	Asn	Asp	His	Asn	Val	Val	Ser	Met	
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Pro	Pro	Ala	Ala	Asp	Val	Lys	His	Thr	Tyr	Thr	Ser	Trp	Asp	Leu	Glu	
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Asp	Met	Glu	Lys	Tyr	Arg	Met	Gln	Ser	Ile	Arg	Arg	Glu	Ser	Arg	Ala	
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Arg	Gln	Lys	Val	Lys	Gly	Pro	Val	Met	Ser	Gln	Tyr	Asp	Asn	Met	Thr	
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Pro	Ala	Val	Gln	Asp	Asp	Leu	Gly	Gly	Ile	Tyr	Val	Ile	His	Leu	Arg	
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Ser	Lys	Ser	Asp	Pro	Gly	Lys	Thr	Gly	Leu	Leu	Ser	Val	Ala	Glu	Gly	
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Lys	Glu	Ser	Arg	His	Ala	Ala	Lys	Ala	Ile	Ser	Pro	Glu	Gly	Glu	Asp	
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Arg	Phe	Tyr	Arg	Arg	His	Pro	Glu	Ala	Glu	Met	Asp	Arg	Ala	His	His	
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His Gly Gly His Gly Ser Thr Gln Pro Glu Lys Pro Ser Leu Pro Gln
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 Lys Gln Ser Ser Leu Arg Ser Arg Lys Leu Pro Asp Met Gly Cys Ser
 1475 1480 1485
 Leu Pro Glu His Arg Ala His Gln Glu Ala Ser His Arg Gln Phe Cys
 1490 1495 1500
 Glu Ser Lys Asn Gly Pro Pro Tyr Pro Gln Gly Ala Gly Gln Leu Asp
 1505 1510 1515 1520
 Tyr Gly Ser Lys Gly Ile Pro Asp Thr Ser Glu Pro Val Ser Tyr His
 1525 1530 1535
 Asn Ser Gly Val Lys Tyr Ala Ala Ser Gly Gln Glu Ser Leu Arg Leu
 1540 1545 1550
 Asn His Lys Glu Val Arg Leu Ser Lys Glu Met Glu Arg Pro Trp Val
 1555 1560 1565
 Arg Gln Pro Ser Ala Pro Glu Lys His Ser Arg Asp Cys Tyr Lys Glu
 1570 1575 1580
 Glu Glu His Leu Thr Gln Ser Ile Val Pro Pro Pro Lys Pro Glu Arg
 1585 1590 1595 1600
 Ser His Ser Leu Lys Leu His His Thr Gln Asn Val Glu Arg Asp Pro
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 Ser Val Leu Tyr Gln Tyr Gln Pro His Gly Lys Arg Gln Ser Ser Val
 1620 1625 1630
 Thr Val Val Ser Gln Tyr Asp Asn Leu Glu Asp Tyr His Ser Leu Pro
 1635 1640 1645
 Gln His Gln Arg Gly Val Phe Gly Gly Gly Gly Met Gly Thr Tyr Val
 1650 1655 1660
 Pro Pro Gly Phe Pro His Pro Gln Ser Arg Thr Tyr Ala Thr Ala Leu
 1665 1670 1675 1680
 Gly Gln Gly Ala Phe Leu Pro Ala Glu Leu Ser Leu Gln His Pro Glu
 1685 1690 1695
 Thr Gln Ile His Ala Glu
 1700

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 <213> Homo sapiens

Pro Phe Gln Gln Val Gly Arg Cys Asn Pro Ser Pro Gln Thr Arg Pro
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Gly Pro Ala Ser Lys Val Lys Gln Asp Met Pro Pro Pro Gly Gly Tyr
20 25 30

Gly Pro Ile Asp Tyr Lys Arg Asn Leu Pro Arg Arg Gly Leu Ser Gly
35 40 45

Tyr Ser Met Leu Ala Ile Gly Ile Gly Thr Leu Ile Tyr Gly His Trp
50 55 60

Ser Ile Met Lys Trp Asn Arg Glu Arg Arg Arg Leu Gln Ile Glu Asp
65 70 75 80

Phe Glu Ala Arg Ile Ala Leu Leu Pro Leu Leu Gln Ala Glu Thr Asp
85 90 95

Arg Arg Thr Leu Gln Met Leu Arg Glu Asn Leu Glu Glu Glu Ala Ile
100 105 110

Ile Met Lys Asp Val Pro Asp Trp Lys Val Gly Glu Ser Val Phe His
115 120 125

Thr Thr Arg Trp Val Pro Pro Leu Ile Gly Glu Leu Tyr Gly Leu Arg
130 135 140

Thr Thr Glu Glu Ala Leu His Ala Ser His Gly Phe Met Trp Tyr Thr
145 150 155 160

<211> 396

<212> PRT

<213> Homo sapiens

Arg Ala Gln Glu Ala Ala Ala Ala Ala Ala Asp Gly Pro Pro Ala Ala
5 10 15

Asp Gly Glu Asp Gly Gln Asp Pro His Ser Lys His Leu Tyr Thr Ala
20 25 30

Asp Met Phe Thr His Gly Ile Gln Ser Ala Ala His Phe Val Met Phe
35 40 45

Phe Ala Pro Trp Cys Gly His Cys Gln Arg Leu Gln Pro Thr Trp Asn
50 55 60

Asp Leu Gly Asp Lys Tyr Asn Ser Met Glu Asp Ala Lys Val Tyr Val
65 70 75 80

Ala Lys Val Asp Cys Thr Ala His Ser Asp Val Cys Ser Ala Gln Gly
 85 90 95
 Val Arg Gly Tyr Pro Thr Leu Lys Leu Phe Lys Pro Gly Gln Glu Ala
 100 105 110
 Val Lys Tyr Gln Gly Pro Arg Asp Phe Gln Thr Leu Glu Asn Trp Met
 115 120 125
 Leu Gln Thr Leu Asn Glu Glu Pro Val Thr Pro Glu Pro Glu Val Glu
 130 135 140
 Pro Pro Ser Ala Pro Glu Leu Lys Gln Gly Leu Tyr Glu Leu Ser Ala
 145 150 155 160
 Ser Asn Phe Glu Leu His Val Ala Gln Gly Asp His Phe Ile Lys Phe
 165 170 175
 Phe Ala Pro Trp Cys Gly His Cys Lys Ala Leu Ala Pro Thr Trp Glu
 180 185 190
 Gln Leu Ala Leu Gly Leu Glu His Ser Glu Thr Val Lys Ile Gly Lys
 195 200 205
 Val Asp Cys Thr Gln His Tyr Glu Leu Cys Ser Gly Asn Gln Val Arg
 210 215 220
 Gly Tyr Pro Thr Leu Leu Trp Phe Arg Asp Gly Lys Lys Val Asp Gln
 225 230 235 240
 Tyr Lys Gly Lys Arg Asp Leu Glu Ser Leu Arg Glu Tyr Val Glu Ser
 245 250 255
 Gln Leu Gln Arg Thr Glu Thr Gly Ala Thr Glu Thr Val Thr Pro Ser
 260 265 270
 Glu Ala Pro Val Leu Ala Ala Glu Pro Glu Ala Asp Lys Gly Thr Val
 275 280 285
 Leu Ala Leu Thr Glu Asn Thr Phe Asp Asp Thr Ile Ala Glu Gly Ile
 290 295 300
 Thr Phe Ile Lys Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Thr Leu
 305 310 315 320
 Ala Pro Thr Trp Glu Glu Leu Ser Lys Lys Glu Phe Pro Gly Leu Ala
 325 330 335
 Gly Val Lys Ile Ala Glu Val Asp Cys Thr Ala Glu Arg Asn Ile Cys
 340 345 350
 Ser Lys Tyr Ser Val Arg Gly Tyr Pro Thr Leu Leu Leu Phe Arg Gly
 355 360 365

His Arg Phe Val Leu Ser Gln Ala Lys Asp Glu Leu
385 390 395

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Ala Glu Met Asp Pro Leu Arg Ala Gln Gln Leu Ala Ala Glu Leu Glu
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Arg Lys Cys Val Pro Pro His Tyr Lys Glu Ala Glu Leu Ser Lys Gly
35 40 45

Glu Ser Val Cys Leu Asp Arg Cys Val Ser Lys Tyr Leu Asp Ile His
50 55 60

Glu Arg Met Gly Lys Lys Leu Thr Glu Leu Ser Met Gln Asp Glu Glu
65 70 75 80

Leu Met Lys Arg Val Gln Gln Ser Ser Gly Pro Ala
85 90

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<210> 438
<211> 303
<212> PRT
<213> Homo sapiens
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Lys Asn Pro Ala Lys Met Ser Leu Tyr Pro Ser Leu Glu Asp Leu Lys
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Val Asp Lys Val Ile Gln Ala Gln Thr Ala Phe Ser Ala Asn Pro Ala
20 25 30

Asn Pro Ala Ile Leu Ser Glu Ala Ser Ala Pro Ile Pro His Asp Gly
35 40 45

Asn Leu Tyr Pro Arg Leu Tyr Pro Glu Leu Ser Gln Tyr Met Gly Leu
50 55 60

Ser Leu Asn Glu Glu Glu Ile Arg Ala Asn Val Ala Val Val Ser Gly
65 70 75 80

Ala Pro Leu Gln Gly Gln Leu Val Ala Arg Pro Ser Ser Ile Asn Tyr

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<211> 378
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<213> Homo sapiens

<400> 439
Val Val Pro Ser Thr Lys Asp Phe Leu Val Gly Val Lys Gly Ser Gly
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Gly His Arg Gly Gly Gly Glu Met Ala Phe Ser Gly Ser Gln Ala Pro
          20                      25                      30

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Tyr	Leu	Ser 35	Pro	Ala	Val	Pro	Phe	Ser	Gly	Thr	Ile	Gln	Gly	Gly	Leu
Gln	Asp 50	Gly	Leu	Gln	Ile	Thr	Val	Asn	Gly	Thr	Val	Leu	Ser	Ser	Ser
Gly 65	Thr	Arg	Phe	Ala	Val 70	Asn	Phe	Gln	Thr	Gly 75	Phe	Ser	Gly	Asn	Asp 80
Ile	Ala	Phe	His	Phe 85	Asn	Pro	Arg	Phe	Glu 90	Asp	Gly	Gly	Tyr	Val 95	Val
Cys	Asn	Thr	Arg 100	Gln	Asn	Gly	Ser	Trp 105	Gly	Pro	Glu	Glu	Arg	Lys	Thr
His	Met	Pro 115	Phe	Gln	Lys	Gly	Met 120	Pro	Phe	Asp	Leu	Cys 125	Phe	Leu	Val
Gln	Ser 130	Ser	Asp	Phe	Lys	Val 135	Met	Val	Asn	Gly	Ile 140	Leu	Phe	Val	Gln
Tyr 145	Phe	His	Arg	Val	Pro 150	Phe	His	Arg	Val	Asp 155	Thr	Ile	Ser	Val	Asn 160
Gly	Ser	Val	Gln	Leu 165	Ser	Tyr	Ile	Ser	Phe 170	Gln	Asn	Pro	Arg	Thr 175	Val
Pro	Val	Gln 180	Pro	Ala	Phe	Ser	Thr 185	Val	Pro	Phe	Ser	Gln	Pro	Val	Cys
Phe	Pro 195	Pro	Arg	Pro	Arg	Gly	Arg 200	Arg	Gln	Lys	Pro	Pro 205	Gly	Val	Trp
Pro 210	Ala	Asn	Pro	Ala	Pro	Ile 215	Thr	Gln	Thr	Val	Ile 220	His	Thr	Val	Gln
Ser 225	Ala	Pro	Gly	Gln	Met 230	Phe	Ser	Thr	Pro	Ala 235	Ile	Pro	Pro	Met	Met 240
Tyr	Pro	His	Pro	Ala 245	Tyr	Pro	Met	Pro	Phe 250	Ile	Thr	Thr	Ile	Leu	Gly 255
Gly	Leu	Tyr	Pro 260	Ser	Lys	Ser	Ile	Leu 265	Leu	Ser	Gly	Thr	Val 270	Leu	Pro
Ser	Ala 275	Gln	Arg	Phe	His	Ile	Asn 280	Leu	Cys	Ser	Gly	Asn 285	His	Ile	Ala
Phe 290	His	Leu	Asn	Pro	Arg	Phe 295	Asp	Glu	Asn	Ala	Val 300	Val	Arg	Asn	Thr
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